RECENT ADVANCES IN ORGANIC CHEMISTRY

FIFTH EDITION

BY

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VOLUME I

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RECENT ADVANCES IN ORGANIC CHEMISTRY

VOLUME I

GENERAL PREFACE

In the present edition, the book which has hitherto been published in one-volume form appears in a new shape, and some explanation of the change appears desirable here.

Since 1908, as the work has passed from edition to edition, my attempt has always been to furnish sufficient fundamental information to allow the reader to appreciate with ease the bearing of the more recent researches, and also to preserve a proper perspective into which the newest facts can be fitted. In order to make room for fresh facts without swelling the size of the volume unduly, I have been forced to discard material from each edition in the preparation of its successor. Had it not been for the limitation in size which was imposed on the volume, the major part of this eliminated material would have been retained permanently; and I have always regretted the compulsory rejection of certain chapters.

In the preparation of this fifth edition, it became clear that further progress along the old lines was now impossible. So much space had to be devoted to newer lines of research, and to completing the accounts of recent work in older branches, that some of the fundamental basis of the subject would have to be rejected in order to make room for new material; and I foresaw the probability that if this were done, the work would degenerate into a mere series of scrappy summaries lacking in any instructive value.

To avert this, the book is now issued in two volumes. In the first of these, a series of themes is treated, which forms a basis for the understanding of some of the newer investigations. At the beginning of the volume I have reprinted (though with considerable revision) the historical chapter which served as an introduction to the first edition, and which contains a

survey of organic chemistry's development during the latter half of the nineteenth century. The corresponding chapter in Volume II. continues the narrative up to the present. In Volume I. I have re-inserted, in their proper places in the general scheme of the book, the chapters on addition reactions and unsaturation which were withdrawn from recent editions purely owing to lack of space. Several critics have expressed regret at the disappearance of these chapters; and I feel that they will serve a useful purpose; so I have revised them and fitted them into the contents.

The first volume of the present edition forms an introduction to the second, but it has a unity of its own, and will be found to contain material suitable for third-year students.

The second volume is intended for Honours students and post-graduate workers. It contains a description of the latest researches in several fields of interest in modern organic chemistry. In some of these the main work of clearing up the subject has been completed, whilst in others the problems are still unsolved, and all that can be done is to give some account of the present-day position.

The two volumes, in conjunction with my book on Stereochemistry, give within reasonable compass a conspectus of the main problems of organic chemistry.

I wish to thank Dr. D. N. M'Arthur and Dr. Hugh Graham for their invaluable assistance in reading the proofs of both volumes and for the suggestions they have made for improving the text.

ALFRED W. STEWART.

PREFACE TO VOLUME I

This volume contains a survey of numerous fundamental problems of organic chemistry, and, with some few exceptions, it deals with subjects upon which general agreement has now been reached. Though complete in itself, it is intended to serve as a framework to which the reader can attach the more outlying subjects which are treated in Volume II. so that he may view these newer fields in proper perspective in their relation to the remainder of the science.

With this object, the present volume opens with an historical survey dealing with the main lines along which organic chemistry progressed during the latter half of the nineteenth century, some of which are described in detail in later chapters.

The second and third chapters, on new reagents and addition reactions, are inserted at this point since some of the material in them has direct application in the constitutional problems discussed in the remainder of the book.

The chapter on the aliphatic diazene compounds, which comes next, was written partly on account of the interest which these compounds present on their own account, and partly because of the kinship in quality between the diazene derivatives and the ketens, which form the subject of the following chapter.

The ketens and the polyketides, which are described in Chapters V. and VI., are closely related to each other; and the description of them forms an introduction to the theories of natural syntheses which are outlined in Volume II.

The next three chapters deal with the constitutions of the monocyclic, dicyclic, and olefinic terpenes. The succeeding three chapters contain an account of the commoner alkaloids,

stress being placed upon those of which the constitutions have been fully elucidated. Chapter XIII. describes the polypeptides and their relations with the proteins. It will be seen that this central portion of the volume contains a survey of naturally-occurring materials.

Finally, the theoretical side of the subject is again touched in the chapters on trivalent carbon, unsaturation, and the problem of substitution in the benzene nucleus. In these, as well as in the chapter on addition reactions, the object has been mainly to supply the reader with food for thought, and examples of the reasoning employed in constitutional questions, rather than merely to catalogue theories; and it is hoped that the insight gained into the complexities of the problems will prove stimulating.

Footnotes are indicated by asterisks, etc., while references to the literature are shown by small figures. This will enable the reader to distinguish between them and save him unnecessary trouble. The abbreviations of journal titles are those used by the Chemical Society.

ALFRED W. STEWART.

The Sir Donald Currie Laboratories,
The Queen's University of Belfast,
October, 1926.

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RECENT ADVANCES IN ORGANIC CHEMISTRY

CHAPTER I

SOME MAIN CURRENTS IN ORGANIC CHEMISTRY

In the observational and experimental sciences, progress can be accomplished only at the cost of destroying or modifying current theories: for if a theory suffices to explain facts discovered after its promulgation, knowledge may be increased; but there is no true progress unless our general outlook is altered. Thus in science there appears an alternation of two processes: in the first, the aim is the accumulation of facts and yet more facts; while the second is directed towards classifying these facts in the most convenient manner. At irregular intervals some facts are discovered which cannot be fitted into the accepted scheme of arrangement; and in order to make room for them the scheme has to be altered and recast into some new form.

In every science which is at all progressive there must arise from time to time conflicts between the older generation of workers and the leaders of the new; for, to those who have grown up along with it, a theory generally becomes invested with a sanctity which is quite out of keeping with its true make-shift character. The longer a theory stands, the harder it is to shake it, and the greater is the tendency of science to become stereotyped. There is another side to the matter. Without any disrespect, it may be said that the majority of scientific investigators are not possessed of strikingly original minds—we cannot all be Pasteurs—and hence there is a very pronounced tendency to take things as they are and work along the beaten track rather than to push

out in the wilderness and risk the chance of losing the road altogether. Thus round every theory there grows up a little band of workers, whose one aim seems to be to accumulate evidence confirming their favourite hypothesis; and in this way the theory gains a considerable weight of supporting data. On the other hand, the solitary worker who happens to differ from the majority of his fellows has to overcome a tremendous weight of unconscious prejudice before he is able to obtain even the semblance of an impartial hearing. In spite of these difficulties, however, progress is made.

Chemistry has proved no exception to the general rule. From the time of the phlogiston theory onwards, the subject has been intermittently developing; older theories have been reluctantly abandoned; and a gradual change of standpoint can be traced, each advance being forced upon the chemist by the impossibility of bringing new facts into line with the older views.

In the history of the origin and growth of scientific theories it is curious to note how certain ideas seem to pervade men's minds at a given period, though they may remain unformulated for some years to come. Again and again it has been found that two investigators have independently pursued the same line of thought, and even accumulated vast stores of facts with regard to the same subject, before any suggestion has been put forward publicly. When these cases are more closely scrutinized, it is often possible to trace the evolution of the idea far farther back than seemed probable at the time. The independent investigators themselves may have been unaware of the existence of previous suggestions which bore upon their views; but one can hardly avoid the view that at given periods certain ideas are "in the air," having been carried so far by previous workers that the new view forces itself upon several minds simultaneously.

Such a crisis occurred in organic chemistry almost half a century ago when the foundations of our modern structural theory were laid. Up to that time the theory of types had served as a stop-gap, but it was too clumsy and inflexible to respond to the ever-growing needs of a rapidly developing science. Only those who have had to refer frequently to papers written previous to 1860, and who have been forced to transliterate the older formulæ into those employed at the present day, can have any idea of the tremendous change brought about by the work of

Frankland,[1] Couper,[2] and Kekulé.[3] We may commence the present survey with the period immediately preceding the publication of Kekulé's first paper on benzene.

Though the formulæ of Couper and Kekulé proved most powerful weapons in the hands of those chemists who were engaged in investigations of aliphatic substances, the equally important class of aromatic bodies still remained in a state of confusion equal to that which prevailed under the type theory. It was the far-sightedness of Kekulé which brought this to an end within less than a decade by a further advance along structural lines. In 1865 he published a paper on this subject;[4] and a year later the whole problem was thoroughly examined by him in a treatise[5] which is probably as fine a piece of reasoning as has yet been devoted to a chemical question.

Kekulé took as his first premise the fact that every aromatic compound contains at least six carbon atoms; secondly, when a compound contains more than six carbon atoms it is often possible to break it down into one containing six carbon atoms, and further decomposition is resisted at this point, which appears thus sharply to mark a definite stage in the process. From these two facts he was led to imagine that there was something in the arrangement of these six carbon atoms which differentiated them from six carbon atoms grouped as in an aliphatic substance. Another step completed the new theory. Having advanced so far, Kekulé had but to ask himself in what way one could arrange six atoms so that they would not form an open chain; and it is now obvious that the simplest reply is, in a ring. To us to-day, this seems such a self-evident solution that we are apt to overlook the greatness of the discoverer and to imagine that "any fool could have done it." There is a certain element of truth in this, for it is apparent that such a discovery might quite well have been the result of a chance idea; in fact, Kekulé himself uses language which might give colour to this view, though probably he did not intend to convey that impression. But Kekulé was not content with a mere statement of the problem's solution; he was able to forecast at once the line of research which

[1] Frankland, *Phil. Trans.*, 1852, **142**, 417.
[2] Couper, *Phil. Mag.*, 1858, IV. **16**, 104.
[3] Kekulé, *Annalen*, 1858, **106**, 129.
[4] Kekulé, *Bull. soc. chim.*, 1868, **1**, 98.
[5] Kekulé, *Annalen*, 1866, **137**, 129.

would have to be followed if the theory were to be put to the test of experiment.

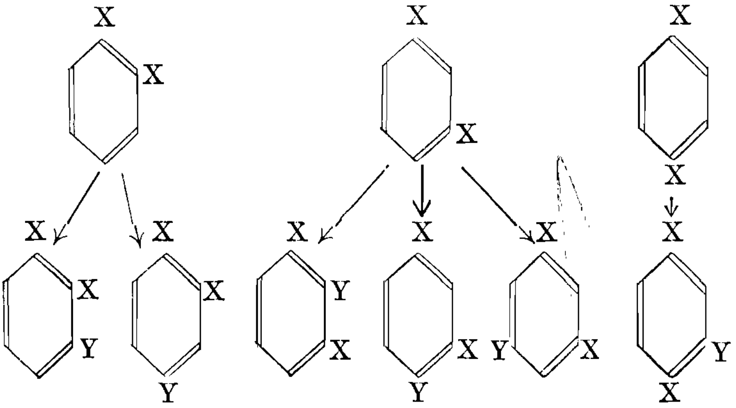
First, however, Kekulé had to explain how the six carbon atoms in the benzene ring could be linked together and united with the six hydrogen atoms which are needed to make up the complete benzene molecule. One of his early views was speedily found to be untenable, as it presupposed two sets of hydrogen atoms—three and three—so placed that a mono-substituted benzene derivative might occur in two isomeric forms. In its final guise, the benzene ring was written practically as we write it now, with a double bond between every alternate pair of carbon atoms and single bonds between the other pairs.

At the time the benzene theory was developed, however, the data which had been accumulated with regard to aromatic compounds were not sufficiently numerous to establish definitely its truth or error. But the new view gave such a stimulus to the investigators of that period that in a very short time it was shown beyond a doubt that the Kekulé theory was capable of furnishing an interpretation of all the facts which had previously been incapable of any clear arrangement.

No sooner had the benzene formula proved its value in this way than a new problem was mooted. Given the benzene ring, it is obvious, as Kekulé himself pointed out in his paper already referred to, that there must be a certain fixed number of isomers for each substituted benzene derivative. For instance, if the substituent introduced is always the same, there will be one mono-substitution product, three di-substitution products, three tri-substitution products, and so forth. The question now at issue was the possibility of determining the constitution of any given isomer; or, in other words, if a poly-substituted benzene derivative were produced in any reaction, what means must be employed to discover the order in which the hydrogen atoms and the substituents lay around the ring.

The investigator who contributed most to the development of this section of the subject was Kekulé's pupil, Körner. If into the ring of a di-derivative of benzene one additional substituent be introduced (thus forming a tri-derivative), it will be found that the number of possible tri-derivatives depends upon the constitution of the di-derivative from which the start was made. As can be seen from the figures below, an *ortho*

di-derivative will yield two tri-derivatives, a *meta* di-derivative gives three tri-derivatives, while from a *para*-compound only one tri-derivative is formed. The relations of the tri-derivatives among themselves can be established by an analogous method.



Körner, Griess, Ladenburg, Graebe, and Baeyer all aided to establish the relations between the different substitution products of benzene, and in a comparatively short space the filiation between all the various classes of benzene derivatives had been made clear.

It is a curious study to track down in the early controversies on the constitution of benzene the germs of other theories which came later to their full development. One instance will suffice here. Ladenburg[1] was the first to point out that while *ortho*-di-substituted benzene derivatives occurred in one form only, the Kekulé hexagonal formula permitted two, which can be expressed by the formulæ below. In the one case the carbon atoms carrying the substituents are joined by a double, in the other case by a single, bond—

[1] Ladenburg, *Ber.*, 1869, **2**, 140.

Ladenburg adduced the supposed parallel cases of crotonic and vinyl-acetic acids, which differ in the position of the double bond with reference to the carboxyl group—

$CH_3—CH : CH—COOH$	Crotonic acid.
$CH_2 : CH—CH_2—COOH$	Vinyl-acetic acid.

He alleged that if the shift of a linkage made no change in benzene, it should be equally without effect in the case of these two substances. But as they actually existed in isomeric forms, the same was to be expected in benzene, if the Kekulé theory were correct.

Ladenburg was answered by Kekulé,[1] also by Victor Meyer.[2] The latter pointed out that while in benzene the only difference between the two hypothetical isomeric forms was produced by a mere change in the grouping of linkages, the cases of the two acids shown above were further complicated by the fact that a hydrogen had also shifted its position from the end of the chain to the carbon atom next the carboxyl group. Thus the cases of benzene and the unsaturated acids are not really analogous at all.

Kekulé attacked the Ladenburg view from a different standpoint, as follows :—

> " The atoms of the systems which we call molecules must be considered to be continually in motion. This view has often been expressed by physicists and chemists, and I have already discussed it in my handbook. Hitherto no explanation as to the form of this intramolecular motion has been given, as far as I know. Chemistry must, at all events, bring forward the claim that such a mechanical hypothesis accounts for the law of the linking of atoms. A planetary motion seems, therefore, not inadmissible ; the movement must be of such a kind that all the atoms forming the system retain the same relative arrangement—in other words, that they return to a mean position of equilibrium. If we now select from the numerous conceptions which may be formed, that which gives the most complete account of the chemical claims and which coincides most closely with the hypothesis of modern physicists as to the mode of the motion of molecules, the following assumption will appear the most probable.
>
> " The simple atoms of the system approach each other in what may be considered a straight line, and rebound like elastic bodies. What we call valency would then have a mechanical meaning. Valency is the number of contacts experienced by one atom on the part of other atoms in unit time. In the same time that the monad atoms of a diatomic molecule

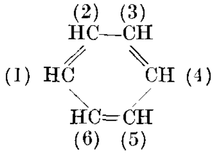
[1] Kekulé, *Annalen*, 1872, **162**, 87.
[2] V. Meyer, *Annalen*, 1870, **156**, 265 ; 1871, **159**, 24.

strike each other once, the dyad atoms of a diatomic molecule come twice into contact with each other, the temperature being the same in both cases. In a molecule made up of one dyad and two monads the number of contacts, under the same conditions, in unit time is two for the dyad and one for each monad atom.

"If two atoms of tetrad carbon are linked together by one combining unit of each, they strike together once in unit time, or in the same time that a monad hydrogen atom makes a complete vibration. During this time they encounter three other atoms. Carbon atoms, which we call doubly linked, come in contact twice in unit time, and further in the same period collide twice with other atoms.

"If we now apply these views to benzene, the formula which I have proposed appears as an expression of the following conception. Each carbon atom strikes against two others in unit time, once against one and twice against the other. In the same unit of time it comes once into contact with hydrogen and completes one vibration.

"If we now represent benzene by the hexagon formula and fix our attention on one of the carbon atoms (that marked 1, for instance)—



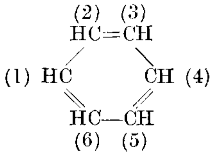
we can express the contacts it experiences during the first unit of time by—

(I.) 2, 6, *h*, 2,

where *h* stands for the hydrogen atom. In the second unit of time that carbon atom which has just encountered No. 2 turns next to No. 6. Its collisions during the second unit of time are—

(II.) 6, 2, *h*, 6.

While the contacts during the first unit of time are represented by the hexagonal arrangements above, those during the second unit of time are represented by—



The same carbon atom, therefore, is during the second unit of time doubly linked to one of the adjoining carbon atoms, while during the second unit of time it is in double linkage with the other carbon atom.

"The most simple mean of all the contacts of one carbon atom is found from the sum of the contacts during the first two units of time, which then repeat themselves periodically—

2, 6, *h*, 2, 6, 2, *h*, 6 . . . .

and we see now that each carbon atom strikes against the two others with which it is directly combined, an equal number of times ; in other words, it bears the same relation to each of its neighbours. The ordinary formula for benzene only represents the contacts made during the first unit of time, or only one phase, and thus the view has sprung up that the di-derivatives with the positions 1, 2 and 1, 6 must be different. If the above hypothesis or any similar one be considered to be correct, it follows that this difference is only apparent, not real."

Thus early in the history of modern structural chemistry did the vibrational hypothesis make its appearance, and from that time to the present day the view has slowly grown that the intramolecular arrangement of atoms can best be represented by a series of vibration phases rather than as a rigid assemblage of particles.

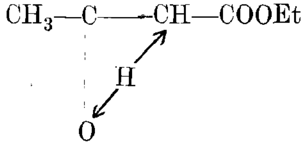
The next stage in the evolution of this theory was reached from quite different evidence. The Kekulé benzene oscillation had been put forward to explain why two apparently different structures had the same properties ; but in the question of the acetoacetic ester constitution, which came to the front soon after this, the crux of the problem lay in the fact that one substance reacted as if it had either one or other of two totally different structures.

In 1876 Butlerow [1] was led to suggest that in certain compounds a kind of intramolecular vibration was continually taking place, which explained why some substances reacted now in one way and again in another according to the type of reagent with which they were treated. Some years later, Laar [2] collected a number of cases in which, by shifting a hydrogen atom from one atom to another in a formula, it was possible to give some idea of how the substances were able to act as if they had two different constitutions. For instance, in the case of acetoacetic ester it is found that with certain reagents it acts as if it contained a hydroxyl group, while with other substances it behaves as if it were a pure ketonic compound. This can be expressed by saying that in the one instance it reacts as if it had formula (I.), while in the other it appears to have the structure (II.)—

$$\text{(I.)}\ CH_3\text{—}\underset{\displaystyle OH}{\underset{|}{C}}:CH\text{—}COOEt \qquad \text{(II.)}\ CH_3\text{—}\underset{\displaystyle O}{\underset{\|}{C}}\text{—}CH_2\text{—}COOEt$$

[1] Butlerow, *Annalen*, 1876, **189**, 76.
[2] Laar, *Ber.*, 1885, **18**, 648 ; 1886, **19**, 730.

This behaviour might be explained by supposing that what we call acetoacetic ester is really a mixture of the two structure isomers (I.) and (II.). Laar took a different view. According to him, acetoacetic ester was a simple substance ; but instead of the hydrogen atom being attached either to the carbon or to the oxygen atom, it wandered or vibrated in space between them, and was finally influenced in its choice of position by the action of the reagent applied to the acetoacetic ester. This may be represented by the following picture :—



Substances of this type Laar proposed to call *tautomeric* (ταὐτό, the same ; μέρος, a part).

This idea of intramolecular vibration, however, soon received an extension by the discovery of cases in which substances not only reacted as if they had two different structures, but could be actually isolated in the two structurally distinct forms. This showed that in some instances at least the Laar hypothesis was incorrect, or, rather, was too narrow a statement of the case ; for instead of the wandering atom remaining always like Mahomet's coffin midway between two extremes, in these examples it was actually to be found at either end of the vibration range. A substitute for the Laar hypothesis was brought forward by Jacobson.[1] In his view, certain substances may occur in either of two structurally different forms, and the change of one form into the other takes place only under the action of some reagent. Since any such change must be produced by a shifting of the bonds within the molecule, Jacobson proposed to describe the phenomenon by the name of *desmotropy* (δεσμός, bond ; τρόπος, change).

Hantzsch and Herrmann [2] suggested that the whole subject should be treated as one ; so that if a substance could be isolated in two stable forms it should be called *desmotropic,* while if it could not be so isolated it should be termed *tautomeric.* The term usually employed nowadays is *dynamic isomerism,* which

[1] Jacobson, *Ber.*, 1887, **20,** 1782 ; 1888, **21,** 2628.
[2] Hantzsch and Herrmann, *Ber.*, 1887, **20,** 2803.

was introduced by Lowry, and the two isomeric forms are called *dynamic isomerides.* Acetoacetic ester has now been proved to be an equilibrium mixture of two dynamic isomerides, one of which has the ketonic, the other the enolic structure.

It would occupy too much space to trace the various developments of this idea through the controversy on the constitution of acetoacetic ester and hence into the field of pseudo-acids and indicators : * but it furnishes one of the most fascinating chapters in the history of organic chemistry ; and the culminating discovery of the action of indicators proved that organic chemistry could hold its own even in the physico-chemical field.

Before these kinetic views on molecular constitution established themselves in the minds of chemists, Baeyer had opened a long series of investigations upon the structure of the benzene molecule. These researches were carried out on the implicit assumption that in the constitutional formula of benzene there was a fixed, unalterable arrangement of valencies which could be inferred from the experimental results of oxidations, reductions, and other reactions. Many different modifications of the benzene hexagon had come into existence, and Baeyer endeavoured to establish, by means of his researches, which one of these actually represented the true formula of benzene. In the end, Baeyer himself was driven to conclude that there is no single formula which will explain all the reactions of the benzene structure. Collie [1] has shown how all the proposed formulæ may be harmonized and expressed by means of a simple vibrational system in three dimensions ; and it seems unlikely that this will be improved upon to any great extent until our views on the electronic structure of carbon compounds have advanced further than the stage which they have reached at present.

From the benzene structure, it is a natural transition to those reduced benzene rings which form the basis of the terpenes and their derivatives ; and after dealing with benzene, Baeyer was led to take up terpene chemistry. To his work in that field much of our present knowledge is due ; but we are even more indebted to Wallach who began work on this subject about the

* An interesting account of the acetoacetic ester controversy is to be found in Lachman's *Spirit of Organic Chemistry.* Pseudo-acids and indicators are dealt with in Stewart's *Physico-chemical Themes.*

[1] Collie, *J.*, 1897, **71**, 1013.

same time as Baeyer. In this connection, some mention must be made of the camphor controversy, which for a decade raged through a corner of the chemical world. Every organic chemist of note seems to have considered himself in duty bound to propose some formula for camphor or a camphor derivative, and the confusion resulting from this prodigality was only banished by Komppa's synthesis of camphoric acid and camphor, which will be described in the chapter upon the dicyclic terpenes.

The reader will now have gained some idea of the extraordinary fertility of the theory of aromatic compounds put forward by Kekulé. We must next turn to another question in which Kekulé, if not the actual originator, was at least one of a long chain of investigators whose work has had a marked influence upon our ideas of intramolecular arrangement.

On looking back upon the work of scientific discovery, one is struck most, not by the fact that certain things have been discovered, but by the very slightness of the barrier which so often stood between the success and failure of a certain line of research at a given period. Again and again subjects have been approached and their problems virtually solved, yet for want of just one connecting link, or even the addition of a few words to a statement which in itself contains the key to the problem, the question may go unanswered for years. No better example of this is to be found than that furnished by the evolution of stereochemical theory.

In 1860 Pasteur [1] carried out an investigation of the tartaric acids, in which he showed that crystals of dextro- and lævo-tartaric acid are related to one another as an object is related to its image in a mirror. At this time the structure theory was in its very infancy, and Pasteur does not seem to have thought of applying it to the case with which he was dealing. He contented himself with putting forward, as a possible explanation, the view that the atoms in the tartaric acid molecule were arranged in right- or left-handed spirals, or were grouped at the corners of a tetrahedron. This was the germ of the whole of modern stereochemistry; but, for want of a slight addition to these expressions, it remained for later investigators to reap the credit of establishing the correctness of this view. In 1869

[1] Pasteur, *Récherches sur la dissymmetrie moléculaire des produits organiques naturels.*

Paternó [1] proposed to explain certain cases of isomerism by means of tetrahedral models. Kekulé,[2] two years previously, had described a tetrahedral model, but it seems doubtful whether he really intended it to convey an idea of the distribution of valencies in four directions in space. No notice was taken of either of these suggestions by the chemical world in general, and it appears to have been Wislicenus [3] to whom we owe the next definite pronouncement on the subject. After proving that the structures of the isomeric lactic acids were identical, he added, "The facts force us to explain the difference between isomeric molecules of the same structure by a different arrangement of atoms in space."

The ultimate solution was published simultaneously by Le Bel [4] and van't Hoff,[5] who pointed out that organic substances showing optical activity contained at least one *asymmetric carbon atom*, *i.e.* an atom with its four valencies attached to four dissimilar groups. Later research suggests that the presence of an asymmetric carbon atom is not essential for the manifestation of optical activity; since the molecule as a whole may be asymmetric (*i.e.* not superposable on its mirror-image) even when no asymmetric carbon atom of the type defined above is present in the structure.

A slight extension of the theory of a tetrahedral grouping of radicles served to account for the occurrence of isomeric substances containing a double bond; and Baeyer [6] applied it also to the case of cyclic substances. But the theory has been by no means limited to carbon compounds. In 1890 Hantzsch and Werner [7] had recourse to stereochemical ideas to explain cases of isomerism among the oximes; in 1893 Werner was able to bring some semblance of order into the class of metal-ammonia derivatives; while in 1894 Hantzsch [8] put forward a theory of the diazo-group. On the side of the question dealing with optical rotatory power, the work of Le Bel,[9] and his successors have

[1] Paternó, *Giorn. di Scienze Naturali ed. Econ.*, V. Palermo, 1869.
[2] Kekulé, *Zeitsch. f. Chem.*, 1867, N.F., **3**, 217.
[3] Wislicenus, *Annalen*, 1873, **167**, 343.
[4] Le Bel, *Bull. soc. chim.*, 1874, II. **22**, 377.
[5] Van't Hoff, *Voorstell tot uitbreiding der structuur formules in de ruimte.* Utrecht, 1874.
[6] Baeyer, *Ber.*, 1885, **18**, 2277.
[7] Hantzsch and Werner, *Ber.*, 1890, **23**, 11.
[8] Hantzsch, *Ber.*, 1894, **27**, 1702.
[9] Le Bel, *Compt. rend.*, 1891, **112**, 724; 1904, **129**, 548; Smiles, *J.*, **1900**.

shown that asymmetric atoms of elements other than carbon may also give rise to activity.

So much for the statical side; but there is another point of view from which the relations between the positions of atoms in space may be regarded. In this new field Victor Meyer and Bischoff contributed by far the greatest additions to our knowledge. They showed that reactions may be hindered, or even completely inhibited, by certain groupings of atoms in given positions. For example, if in benzoic acid we substitute methyl groups for the two hydrogen atoms in the ortho-position to the carboxyl group, the acid becomes at once much more difficult to esterify. This phenomenon is termed *steric hindrance.*

One of the greatest pieces of stereochemical research was opened when Emil Fischer and his students first began methodically to examine the sugars. The investigation of this class of bodies was at that time regarded as one of the most hopeless problems which an organic chemist could set himself. The substances were often uncrystallizable, and differed so little among themselves that it seemed hopeless to try to separate one isomer from a mixture. Further, the great complexity of their isomerism, due to the numerous optical isomerides which are possible, made the attack on this branch of stereochemistry seem one of the least promising. It is easy to believe that with only ordinary means at his disposal Fischer could never have accomplished the work; but his genius had stood him in good stead in one of his earlier researches. In 1877 he discovered the compound phenylhydrazine,[1] and by means of this substance he was able to convert an imperfectly crystallizable sugar into a crystalline phenylhydrazone, from which he was able to regain the sugar after he had thus separated it from its isomers. In a few years Fischer [2] completed this vast research, in the course of which he established the configurations of all the pentoses and hexoses by experimental means and by reasoning which is unlikely to be surpassed for simplicity and directness.

After leaving the sugars, Fischer devoted his attention to the purine group, in which he carried out a series of brilliant

77, 1174; Pope and Peachey, *P.*, 1900, **16,** 42, 116; Pope and Neville, *J.*, 1902, **81,** 1552; Kipping, *J.*, 1907, **91,** 209; Meisenheimer and Lichtenstadt, *Ber.*, 1911, **44,** 356; Werner, *Ber.*, 1911, **44,** 1887.

[1] Fischer, *Annalen*, 1877, **190,** 81. [2] Fischer, *Ber.*, 1894, **27,** 3189.

syntheses,* and when this subject in its turn was exhausted, he attacked the problem of the decomposition products of the peptones, with results which are described in a later chapter of the present volume.†

There are one or two other fundamental problems which should be mentioned here, but they are somewhat disconnected from each other and from the parts of organic chemistry which have just been described.

In the first place, there is the pyridine question. After the constitution of benzene had been established, it was inevitable that the same view would sooner or later be applied to pyridine, and in 1869 Körner ‡ proposed to represent that substance by a benzene ring in which one of the —CH= groups was replaced by a nitrogen atom. This theory was supported by some researches of Kekulé,[1] and is to-day accepted as correct. The importance of pyridine and its simple derivatives does not lie in themselves, but rather in the fact that the pyridine ring appears to form the basis of all the natural alkaloids, just as the benzene ring is the foundation of the aromatic series.

A discovery of much general interest was that of the oxonium salts. Collie and Tickle [2] were the first to establish the fact that oxygen can act as a quadrivalent element and furnish salts which resemble the ordinary ammonium compounds. The wide distribution of the oxonium derivatives among natural products such as the flower pigments renders these oxonium salts of the greatest interest.

Since the time of Kekulé, organic chemistry has been for the most part a synthetic science. At the present day considerably over a hundred thousand organic compounds are known, and one need not have the least hesitation in saying that if seventy per cent. of them had never been synthesized we should not feel the lack of them to any appreciable extent. The origin of this enormous flood of synthetic material is to be found in the German University system; for since, under the

* See Chapter XII.

† See Chapter XIII.

‡ The first publication of this idea seems to be due to Dewar, *Zeit. f. Chem.* 1871, 117.

[1] Kekulé, *Ber.*, 1890, **23**, 564; see also Richter-Anschütz, *Lehrbuch d. Organ. Chemie*, 1905, II. 711, 712.

[2] Collie and Tickle, *J.*, 1899, **75**, 710.

German regulations the degree in chemistry is granted only on the results of original research, it follows that every Ph.D. in organic chemistry represents so many new compounds—at least, as a general rule. But these do not include all the forces leading to the steady pursuit of the synthetic branch. The great German dye industry employs in itself hundreds of chemists, and from them also flows a steady stream of new compounds. The same may be said of the explosive manufacturers and the firms which produce synthetic drugs.

Before closing this chapter a glance may be cast at the physical methods which have sprung up in organic chemistry during the last half-century. The relation between chemical constitution and optical rotatory power dates, of course, from the time of van't Hoff and Le Bel's papers on the asymmetric carbon atom, though a quantitative relation between rotatory power and chemical constitution is still to be sought. Refractive index has been proved to be a property which is closely connected with the mode of linkage of the atoms in organic compounds, and much work has been done in this line by Brühl and others. The electrical conductivities of acids depend very greatly upon the constitution of the radical to which the carboxyl group is attached. Magnetic rotation, *i.e.* the optical rotatory power which nearly all substances acquire when placed in strong magnetic fields, has been studied in great detail by the late Sir W. H. Perkin, who showed that by its aid the constitution of many substances could be determined. Absorption spectra, both optical and electric, have been used in the establishment of doubtful formulæ, the former by Hartley and others, the latter by Drude. Magnetic susceptibility has been worked out by Pascal and proved to be a property depending upon chemical structure. In recent times, the Tesla-luminescence spectra of organic compounds have been discovered by McVicker, Marsh and Stewart, who have shown that here also the constitutional factor plays its part.

In the foregoing brief survey of organic chemistry, it has, of course, been impossible to deal with many pieces of work which are quite as important as some of those actually mentioned, but, on the whole, it is believed that a fairly accurate picture has been given of the evolution of the subject along various lines. If we look only to the principles which lie at the back of the

science and which, though they may remain unformulated, still sway our views by some sub-conscious action, it will appear that the history of the last half-century has been one of a gradual passing from a static to a dynamic view of the molecule. In the early days, the ideas of chemists centred round more or less rigid structures which they regarded as approximately "set." The tetrahedron of van't Hoff had the effect of strengthening rather than weakening this tendency; and it is perhaps unfortunate that van't Hoff's view, rather than that of Le Bel, found favour in the chemical world at large. At this period the state of mind * of the average organic chemist seems to have been somewhat similar to that of the student who, when asked to explain the atomic theory, said, "Atoms are square blocks of wood invented by Dr. Dalton."

This view of the subject was shaken by the publication of Werner's views on affinity and valency,[1] in which the idea of directed valencies was shown to be unnecessary; and at the present day the idea of a certain amount of intramolecular "play" is not regarded as absolute anathema by the more advanced school.

The existence of polar and non-polar valencies was still left unsettled, however. The so-called polar valencies were supposed to be a type which was ruptured by the dissociation of a molecule during the formation of ions; whilst the non-polar type was akin to the carbon valency which normally is incapable of breaking and yielding two oppositely-charged ions. This distinction between two kinds of valency has now been abandoned with the acceptance of G. N. Lewis's electronic conception of the atom, which brings all types of valency into one general scheme.[2] Up to the present, the full implications of the Lewis atom have not been whole-heartedly applied in the field of organic chemistry, as the matter is a complex one; but possibly before long something will be done in this line of thought.

It must be frankly admitted that since the opening of the present century, theoretical organic chemistry has been rather barren in many directions. Much useful work has been done in

* If this statement appears exaggerated, the reader is recommended to consult the *Annalen*, 1901, **316**, 71, where he will find ample evidence of the persistence of these views in certain circles.

1 Werner, *Beiträge zur Theorie der Affinität und Valenz*, 1891.

2 See G. N. Lewis, *Valence* (1923).

the field of natural compounds; but on the theoretical side, the subject has yielded very little beyond some minor ideas, none of which is comparable to the great clarifying of our views which took place between 1850 and 1900. When the recent progress of organic chemistry is compared with the tremendous revolutions in inorganic chemistry and radioactivity which have been brought about by the work of Thomson, Ramsay, Rutherford, Soddy, Aston, and Lewis, the contrast cannot but strike the mind.

One reason for this comparative barrenness is perhaps to be found in the attraction which the newer subjects have exercised upon investigators, drawing the more original minds away from organic problems. The formula of triphenylmethane is certainly a less entrancing subject than, say, the peculiar phenomenon of isosterism; and it is only natural that inquiring intellects should concentrate themselves by preference upon matters which seem more fundamental than problems of molecular structure.

There is, however, no reason to despair of the future of organic chemistry. It is true that the mere synthesis of a large number of new substances or even the clearing-up of the constitution of some intricate alkaloid will not lead to a fresh avatar of the subject. What is urgently needed is a completely new line of development. It is not difficult to suggest ways in which such a change of trend might be accomplished. For example, nine-tenths at least of our laboratory reactions lie outside the temperature-limits under which the plants and the animals exist, yet plants and animals succeed in producing quite considerable yields of certain materials which we can obtain in the laboratory only with some difficulty. It seems not impossible that a study of reactions which can take place at ordinary temperatures and in the absence of violent reagents, might open up an entirely fresh line of development in organic chemistry. Our increased modern knowledge of catalysts and their action makes this field much more promising than it once was; and the possibilities involved in the use of colloidal reagents need only be mentioned in order to suggest lines of investigation which could hardly prove unfruitful.

There is one obvious advantage which would be conferred by a return to nature such as is here suggested. Research of this kind would clearly centre round the very simplest of our

known reactions—the addition or removal of the elements of water: for these two processes evidently play a prominent if not a predominant part in the natural syntheses. Thus some incentive would be given to a study of the mechanism of our simplest chemical changes, a subject which would certainly repay a good deal of investigation.

On the theoretical side, organic chemistry seems at first sight to have reached an almost unnatural perfection so far as main principles go; for few sciences have attained such a high pitch of organization in so short a period. But this state of affairs is not altogether healthy, since it tends to repel original minds who find little interest in a subject which is apparently resting on a dead centre of perfectness. At the present day, it seems fashionable to suppose that certain views are so firmly established that no research into their foundations is worth the labour expended on it; and consequently a large number of investigators devote their energies to the examination of highly complex substances because they assume that the simpler compounds have been "worked out." In the same way, it was supposed for many years that the composition of the atmosphere was definitely settled—and then the discoveries of Rayleigh and Ramsay showed how little was known of even this common mixture. With this object lesson before them, it is to be hoped that more organic chemists will find time to investigate some of the problems which are passed over by the bulk of workers who seem to place a label in the same category as an explanation.

CHAPTER II

SUNDRY MODERN REAGENTS

WITH the exception of oxidizing and reducing agents, the reagents of organic chemistry are, as a general rule, specific in character: they attack one particular characteristic portion of the molecule, such as the hydroxyl group or the carbonyl radicle, leaving the remainder unaffected. Thus any survey of newer reagents can only give the impression of a series of disjointed data, since the reactions in the majority of cases do not hinge on to each other to form a connected scheme. The one exception to this is the case of the Grignard reagent, which is probably the most generally applicable of all the synthetic agents at present at our disposal, since it attacks a whole series of the characteristic groups of organic compounds.

1. *The Grignard Reagent*

In view of the advantages conferred on synthetic chemistry by the discovery of the alkyl derivatives of zinc, it is strange that thereafter a whole generation elapsed before the properties of the corresponding magnesium compounds were carefully examined.

In 1899, Barbier,[1] by treating an ethereal solution of methyl-heptenone with magnesium and methyl iodide, produced a compound containing magnesium which was decomposed by water and yielded the corresponding alcohol, dimethyl-heptenol. Recognizing the possible value of this reaction, Barbier suggested to Grignard that it was worthy of further study.

Grignard[2] found that when an alkyl iodide diluted with anhydrous ether was allowed to act on magnesium turnings, the metal dissolved and yielded a solution possessing all the

[1] Barbier, *Compt. rend.*, 1899, **128**, 110.
[2] Grignard, *Compt. rend.*, 1900, **130**, 1322.

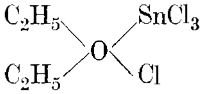
properties of a metallo-organic compound. It was attacked by moist air, decomposed violently when treated with water, and acted upon almost all types of organic compounds.

The constitution of the Grignard reagent is still, after a quarter of a century, a matter of dispute; but various views have been suggested which may be briefly summarized here, since the evidence adduced by their authors is of some interest.

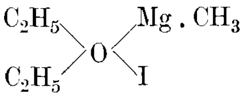
The formula R—Mg—X, where R is an alkyl or aryl radicle and X is a halogen atom, leaves out of account the ether, which apparently plays some part in the reaction.

Grignard,[1] as well as Blaise,[2] put forward the view that the ether acts not merely as a solvent, but exerts besides some influence on the action of the organo-metallic derivative. In support of this it may be pointed out that the Grignard reagent, even when heated to over 100° C. under reduced pressure in a current of hydrogen, retains one molecule of ether. These two authors, from the analogy of water of crystallization, regarded this as a case of "ether of crystallization"; which would be expressed by the formula, $CH_3.Mg.I+(C_2H_5)_2O$.

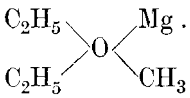
Baeyer and Villiger,[3] however, pointed out that negative metallic chlorides, such as stannic chloride, unite with ether to form oxonium salts of the type:



and by analogy they proposed the formula:



for the combination of ether and magnesium alkyl iodide. Grignard[4] preferred to invert the alkyl radicle and halogen atom in this expression, giving:



[1] Grignard, *Thèse sur les combinaisons organomagnésiennes mixtes.* Lyons, 1901.

[2] Blaise, *Compt. rend.*, 1901, **132**, 839.

[3] Baeyer and Villiger, *Ber.*, 1901, **34**, 2679.

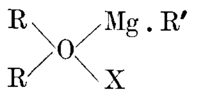
[4] Grignard, *Récents progrès de la chimie*, 1904, p. 128.

In his view, this formula expressed more clearly the resistance of the reagent to the action of sodium and agreed better with the mode of scission of the compound.

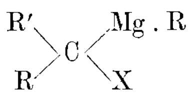
New light was thrown on the whole question by Tschelinzeff [1] who substituted benzene for ether in the reaction-mixture. He found that though the organo-metallic derivative was still formed, it required a much higher temperature than when ether was present. If to the benzene solution a little ether or anisole was added, the reaction took place much more readily; a white compound separated from the solution; and on analysis this substance was found to contain no ether, though in other respects it differed but little from ordinary organo-magnesium derivatives. From this it is obvious that the oxygen compound, ether or anisole, assists the progress of the reaction.

Again, by using anisole, it is possible to prepare ether-free organo-magnesium derivatives and then measure the heat evolved when ether is added to these materials. Tschelinzeff [2] found that on the average in benzene solution the addition of ether liberates about twelve Calories. He inferred that the formation of the Grignard reagent occurs in two stages: in the first, the simple organo-magnesium salt is produced, which, in the second stage, unites with ether to form an addition-compound.

Tschelinzeff [3] stated that it is possible to prepare *two* sets of oxonium compounds and study their decomposition with water; and on this ground he suggests that the Baeyer and Villiger formula for these compounds must be the correct one, as it allows the possibility of two isomers:



and



Grignard [4] prefers his own formula, which also allows of the existence of isomerides, on the ground that it makes clear certain intramolecular changes.

Before leaving the question of the oxonium derivatives, it may be well to mention another view of their constitution

[1] Tschelinzeff, *Ber.*, 1904, **37**, 4534; *Chem. Zeit.*, 1906, **30**, 378; compare Brühl, *Ber.*, 1903, **36**, 668; 4272; 1904, **37**, 746; Malmgren, *ibid.*, 1903, **36**, 2608.

[2] Tschelinzeff, *Ber.*, 1905, **38**, 3664.

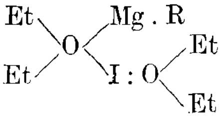
[3] Tschelinzeff, *Compt. rend.*, 1907, **144**, 90.

[4] Grignard, *Bull. soc. chim.*, 1907, IV. **1**, 255.

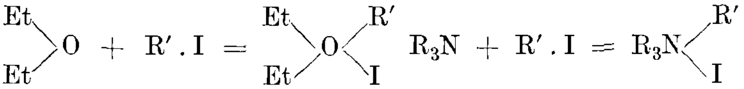
which was put forward by Tschelinzeff. Magnesium iodide combines with either two or four molecules of ether to form complexes, to which the following constitution has been ascribed :—

$$Et_2O : I . Mg . I \quad \text{and} \quad (Et_2O)_2I . Mg . I(Et_2O)_2$$

By analogy with the second formula, Grignard's reagent might have the constitution :

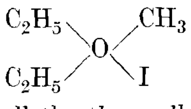


Ethers are not the only substances which can act as catalysts in this reaction, however, for it has been shown that tertiary amines have the same property. Tschelinzeff [1] brought this into line with the case of the others in the following manner. In both cases, he supposed, the first effect of the catalyst is to dissociate the alkyl halide and to form a salt with it :



The metallic magnesium is then assumed to act upon the salts, abstracting the alkyl iodide and forming compounds of the type R′—Mg—I.

An objection against formulæ of the above type can easily be raised. If the case of a combination between ethyl ether and methyl iodide be chosen for the sake of example :

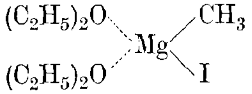


it is obvious that since all the three alkyl groups are similarly attached to the oxygen atom, any one of them might be removed by the magnesium in the next stage of the process, so that the final result would be a mixture of C_2H_5—Mg—I and CH_3—Mg—I; whereas in practice only the last compound is produced.

An attempt has been made to evade this difficulty by bringing in the hypothesis of main and auxilliary valencies.[2] It is assumed

[1] Tschelinzeff, *Ber.*, 1904, **37**, 2081, 4534.
[2] Meisenheimer and Caspar, *Ber.*, 1921, **54**, 1665.

that the co-ordination number of magnesium is 4; and the intermediate addition-product then takes the form:



in which the methyl group and halogen atom are united to the magnesium by main valencies, whilst the ether molecules are attacked by subsidiary valencies.

Enough has been said [1] to show that even in an apparently simple case, the problem of chemical constitution may offer difficulties; and up to the present no generally acceptable view of the Grignard reagent's structure has been put forward.

A study of the relative influences of ether and anisole as solvents has been made by Majima and Kotake,[2] but the details must be sought in the original paper. It appears that when a carbonyl derivative acts on magnesium indole iodide, anisole is the better solvent; but if the reacting compound be an acid chloride, ether as a solvent is preferable.

2. *Some Reactions of the Grignard Reagent with Carbon Compounds* *

The Grignard reagent is applicable to so many different substances that no detailed examination of its behaviour can be given within the limits of a chapter; but all that is necessary here is to select examples of its action upon important types of compounds. For the sake of clearness, it will be convenient to deal with the action of magnesium methyl bromide, $CH_3—Mg—Br$, or phenyl magnesium bromide, $C_6H_5 . Mg . Br$ as examples.

Hydroxyl compounds, Acids and Amines.—When magnesium methyl bromide acts upon substances of the general formula RX, wherein R represents a hydrogen atom or alkyl radicle, whilst X is a halogen atom, hydroxyl radicle, or amino-group, the reaction takes the form of an exchange of places on the part of

[1] For further information, see Braun and Kirschbaum, *Ber.*, 1919, **52**, 1725; Rheinbolt and Roleff, *Ber.*, 1924, **57**, 1921; Meisenheimer, *Annalen*, 1925, **442**, 180.

[2] Majima and Kotake, *J. Chem. Soc. Japan*, 1922, **43**, 936.

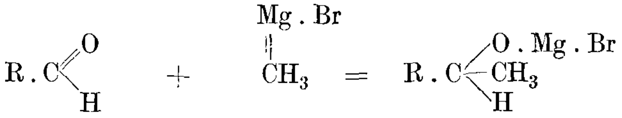
* In view of the enormous literature dealing with this subject, it is impossible to give complete references, and it seems inadvisable to mention a few papers only. The reader desiring full information should consult Houben-Weyl's *Methoden der organischen Chemie*.

the methyl group of the Grignard reagent and the part X of the second molecule, thus :

$$H . OH + CH_3 . Mg . Br = CH_4 + HO . Mg . Br$$
$$H . OC_2H_5 + CH_3 . Mg . Br = CH_4 + C_2H_5O . Mg . Br$$
$$H . Cl + CH_3 . Mg . Br = CH_4 + Cl . Mg . Br$$
$$C_2H_5 . Cl + CH_3 . Mg . Br = CH_3 . C_2H_5 + Cl . Mg . Br$$
$$H . NH_2 + CH_3 . Mg . Br = CH_4 + NH_2 . Mg . Br$$
$$H . NH . C_2H_5 + CH_3 . Mg . Br = CH_4 + C_2H_5 . NH . Mg . Br$$

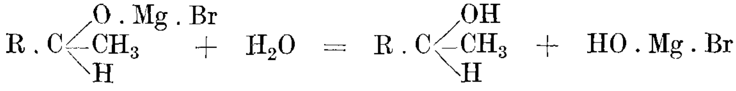
Thus in each of these cases the reaction product is a hydrocarbon.

The Carbonyl Group.—If the molecule acted upon by the Grignard reagent contains a double bond between a carbon and a non-carbon atom, the reaction proceeds in two stages instead of one. In the first stage, the Grignard reagent splits into its organic and inorganic components ; the magnesium atom then attaches itself by its free valency to the *non-carbon* atom at one end of the double bond, whilst the methyl group fixes itself to the carbon atom at the other end of the double linkage, thus :



The reader will note the obvious parallelism between this reaction and the addition of sodium bisulphite and hydrocyanic acid to the carbonyl groups of ketones and aldehydes.

In the second stage of the reaction, the intermediate magnesium compound is decomposed by water and the fragment —Mg . Br is replaced by a hydrogen atom—



It is obvious that, by means of this reaction, a carbonyl derivative can be converted into an alcohol containing a larger number of carbon atoms than the original molecule.

Nitriles and Isonitriles.—When the Grignard reagent is allowed to act upon a compound containing a triple linkage between a carbon and a nitrogen atom, the course of the reaction depends upon the nature of the second reagent. In the case of nitriles, the process takes the same course as in the case of

carbonyl compounds in the first stage, since the magnesium atom attaches itself to the nitrogen :

$$\begin{array}{c}N\\ \||\\ R{-}C\end{array} + \begin{array}{c}Mg.Br\\ |\\ CH_3\end{array} = \begin{array}{c}N.Mg.Br\\ \|\\ R{-}C.CH_3\end{array}$$

The action of water decomposes this intermediate compound and yields as an end-result a ketone :

$$\begin{array}{c}N.Mg.Br\\ \|\\ R.C.CH_3\end{array} + H_2O = \begin{array}{c}O\\ \|\\ R.C.CH_3\end{array} + NH_2.Mg.Br$$

Isonitriles, as might be expected, behave in a wholly abnormal manner ; for in their case both fragments of an aromatic Grignard reagent attach themselves to the quadruply-bound carbon atom, and the final product after treatment with an acid is an aldehyde :

$$R{-}N{\equiv}C + C_6H_5{-}Mg{-}Br = R{-}N{=}C\begin{array}{l}\diagup Mg.Br\\ \diagdown C_6H_5\end{array}$$

$$R{-}N{=}C\begin{array}{l}\diagup Mg.Br\\ \diagdown C_6H_5\end{array} + 2H_2O = R.NH_2 + O:C\begin{array}{l}\diagup H\\ \diagdown C_6H_5\end{array} + HO.Mg.Br$$

Thiocyanates and Isothiocyanates.—In the Grignard reactions of the thiocyanic esters the cyanide radicle is removed bodily in exchange for the methyl group of the methyl magnesium bromide ; and the end-product of the action is an alkyl sulphide :

$$R{-}S{-}CN + CH_3{-}Mg{-}Br = R{-}S{-}CH_3 + CN{-}Mg{-}Br$$

In the case of a Grignard reagent containing an aromatic group instead of an aliphatic one, the reaction yields a mercaptan as the main product :

$$R{-}S{-}CN + C_6H_5{-}Mg{-}Br = C_6H_5{-}CN + R{-}S{-}Mg{-}Br$$
$$R{-}S{-}Mg{-}Br + H_2O = R{-}S{-}H + HO{-}Mg{-}Br$$

The isothiocyanic esters, on the other hand, behave in the normal manner, the magnesium atom attaching itself to the non-carbon atom of the —N=C= bond :

$$\begin{array}{c}R{-}N\\ \|\\ S{=}C\end{array} + \begin{array}{c}Mg.Br\\ |\\ CH_3\end{array} = \begin{array}{c}R{-}N{-}Mg.Br\\ |\\ S{=}C{-}CH_3\end{array}$$

The magnesium-haloid group is then hydrolysed off by water in the form of HO . Mg . Br, leaving CH_3 . CS . NH . R behind. It will be noted that in this reaction the double bond between the carbon and the sulphur atom is not attacked by the Grignard reagent.

Ethers.—Open-chain ethers react with the Grignard reagent only at high temperatures; and when interaction takes place, it follows the course shown below:

$$R'—O—R'' + CH_3—Mg—Br \quad = \quad R'—O—Mg . Br + R''—CH_3$$

Hydrolysis of the intermediate magnesium compound yields as end-products of the reaction the substances R′OH and $R''CH_3$. In practice, a mixture of $R'CH_3$ and $R''CH_3$ is produced, the relative yields depending upon the nature of the radicles R′ and R″.

Cyclic ethers react much more readily than this, yielding primary alcohols:

$$\begin{array}{l} CH_2 \diagdown \\ | \qquad\quad \rangle O \\ CH_2 \diagup \end{array} + \begin{array}{l} Mg . Br \\ \| \\ CH_3 \end{array} = \begin{array}{l} CH_2—O . Mg . Br \\ | \\ CH_2—CH_3 \end{array} \xrightarrow{H_2O} \begin{array}{l} CH_2OH \\ | \\ CH_2 . CH_3 \end{array}$$

Acetals.—In the case of acetals, one of the alkoxyl groups is exchanged for the alkyl group of the Grignard reagent, so that an ether is formed—

$$R . CH(OR')_2 + CH_3 . Mg . Br \quad = \quad R . CH(OR') . CH_3 + R'O . Mg . Br$$

This is a method of obtaining various ethers, according to the nature of the radicles R and R′. Curiously enough, the acetals of formaldehyde react only with difficulty as compared with the higher members of the series.

Nitro-compounds.—This survey of the action of single groups may be closed by a reference to the mode of reaction of the nitro-compounds. As might be expected, the primary and secondary aliphatic nitro-compounds react in the aci-forms: R . CH : NO . OH and R_2C : NO . OH, with the usual result of producing the hydrocarbon corresponding to the radicle in the Grignard reagent. In some cases alkyl-substituted hydroxyl-amines are obtained in the reaction-products. From nitrobenzene and ethyl magnesium iodide, a certain amount of ethyl-aniline is produced by some complex reaction.

Having now dealt with the reactions of the principal characteristic groups, it seems advisable next to examine some cases

in which the molecule contains more than one of these radicles attached to the same carbon atom.

Acid Chlorides.—The group characteristic of the acid chlorides, —CO . Cl, furnishes a simple example of double reaction. In the first stage, there is an exchange of the chlorine atom for the alkyl group of the Grignard reagent, forming a ketone. Another molecule of the Grignard reagent then attacks the ketone, producing a tertiary alcohol:

$$(1)\ R.CO.Cl + CH_3.Mg.Br = R.CO.CH_3 + Cl.Mg.Br$$

$$(2)\ \begin{smallmatrix}R\\CH_3\end{smallmatrix}\!\!>C:O + CH_3.Mg.Br = \begin{smallmatrix}R\\CH_3\end{smallmatrix}\!\!>C<\!\!\begin{smallmatrix}O.Mg.Br\\CH_3\end{smallmatrix} \xrightarrow{H_2O} \begin{smallmatrix}R\\CH_3\end{smallmatrix}\!\!>C<\!\!\begin{smallmatrix}OH\\CH_3\end{smallmatrix}$$

Esters.—The action of the Grignard reagent upon an ester likewise produces a tertiary alcohol, but the progress of the reaction is slightly different from that shown above:

$$(1)\ R.CO.OEt + CH_3.Mg.Br = R—C\!\!\begin{smallmatrix}\diagup CH_3\\ —O.Mg.Br\\ \diagdown OEt\end{smallmatrix}$$

$$(2)\ R—C\!\!\begin{smallmatrix}\diagup CH_3\\ —O.Mg.Br\\ \diagdown OEt\end{smallmatrix} + CH_3.Mg.Br = R—C\!\!\begin{smallmatrix}\diagup CH_3\\ —O.Mg.Br\\ \diagdown CH_3\end{smallmatrix} \xrightarrow{H_2O} R—C\!\!\begin{smallmatrix}\diagup CH_3\\ —OH\\ \diagdown CH_3\end{smallmatrix}$$

Organic Acids.—Organic acids, when treated with the Grignard reagent, also yield tertiary alcohols; but in their case three molecules of the reagent are required for each molecule of acid, since one of the molecules of the reagent is used up in forming a halogen-magnesium salt of the type: R . COO . Mg . Br, which is then further acted on by the Grignard reagent. When salts of organic acids are employed, the reaction goes thus:

$$(1)\ 2R.COOK + 2CH_3.Mg.Br = 2R.CO.CH_3 + (MgBr)_2O + K_2O$$

$$(2)\ 2R.CO.CH_3 + 2CH_3.Mg.Br = 2R.C\!\!\begin{smallmatrix}\diagup CH_3\\ —O.Mg.Br\\ \diagdown CH_3\end{smallmatrix} \xrightarrow{H_2O} 2R.C\!\!\begin{smallmatrix}\diagup CH_3\\ —OH\\ \diagdown CH_3\end{smallmatrix}$$

Acid Anhydrides.—When two molecules of Grignard's reagent act on one molecule of an open-chain acid anhydride, the reaction product is a tertiary alcohol; but from some anhydrides a ketone can be formed by the interaction of equimolecular quantities of the two reagents. In the case of anhydrides of dicarboxylic acids, the Grignard reagent may act in either of two ways. In one case two tertiary alcoholic groups are formed in the molecule, whilst in the other alternative the oxygen bridge is unaffected,

and the two carbonyl oxygens are replaced by two pairs of alkyl groups :

$$(1)\quad (CH_2)_n\left<\begin{array}{l}CO\\CO\end{array}\right>O \xrightarrow{R\,.\,Mg\,.\,Br} (CH_2)_n\left<\begin{array}{l}CR_2\,.\,OH\\CR_2\,.\,OH\end{array}\right.$$

$$(2)\quad (CH_2)_n\left<\begin{array}{l}CO\\CO\end{array}\right>O \xrightarrow{R\,.\,Mg\,.\,Br} (CH_2)_n\left<\begin{array}{l}CR_2\\CR_2\end{array}\right>O$$

Amides.—Under normal conditions, amides break up the Grignard reagent and produce the hydrocarbon corresponding to the alkyl group :

$$R\,.\,CO\,.\,NH_2 + CH_3\,.\,Mg\,.\,Br = R\,.\,CO\,.\,NH\,.\,Mg\,.\,Br + CH_4$$

With excess of the Grignard reagent, however, a second reaction takes place with certain amides, whereby ketones may be formed :

$$R\,.\,CO\,.\,NH\,.\,Mg\,.\,Br + CH_3\,.\,Mg\,.\,Br = R{-}C\!\left<\begin{array}{l}O\,.\,Mg\,.\,Br\\NH\,.\,Mg\,.\,Br\\CH_3\end{array}\right.$$

$$R{-}C\!\left<\begin{array}{l}O\,.\,Mg\,.\,Br\\NH.Mg.Br\\CH_3\end{array}\right. + 2H_2O = R{-}C\!\left<\begin{array}{l}OH\\NH_2\\CH_3\end{array}\right. + MgBr_2 + Mg(OH)_2$$

$$R{-}C\!\left<\begin{array}{l}OH\\NH_2\\CH_3\end{array}\right. = R\,.\,CO\,.\,CH_3 + NH_3$$

In the foregoing examples, two characteristic groups are attached to a single carbon atom. The case of two reactive radicles attached to different carbon atoms in the molecule must now be described. Obviously the main interest in this field is to be found by noting the relative activities of the two characteristic groups.

Halogen-hydrins.—The simplest case is that of the halogen-hydrins. Here the hydroxyl group proves the more reactive. When one molecule of the Grignard reagent is used, the halogen-hydrin behaves like a simple alcohol ; whereas when two molecules of the Grignard reagent act upon one molecule of the halogen-hydrin, both the characteristic groups of the latter come into play :

$$Cl.CH_2.CH_2.OH + C_6H_5.Mg.Br = Cl.CH_2.CH_2.O.Mg.Br + C_6H_6$$

$$Cl.CH_2.CH_2.OH + 2C_6H_5.Mg.Br = C_6H_5.CH_2.CH_2.O.Mg.Br + C_6H_6 + Cl.Mg.Br$$

The first reaction yields the hydrocarbon corresponding to the radicle of the Grignard reagent; the second gives a mixture of this with a substituted alcohol.

When the carbonyl group is present along with other active groups in a molecule, various results may follow the action of Grignard's reagent.

Halogen-substituted Ketones.—In the case of halogen-substituted ketones, the halogen atom in most cases displays the same inertness as in the halogen-hydrins, and the Grignard reagent first attacks the carbonyl group, yielding a halogen-substituted tertiary alcohol. For example, the main product of the interaction between ethyl magnesium bromide and chloro-acetone is the alcohol:

$$Cl\,.\,CH_2\,.\,\underset{HO\diagup\ \diagdown C_2H_5}{C}\,.\,CH_3$$

Hydroxy-ketones.—With hydroxy-ketones, the reaction may occur in two stages. The first step is the exchange of the hydroxylic hydrogen for the magnesium halide nucleus of the Grignard reagent and the production of the hydrocarbon corresponding to the Grignard radicle. Thereafter, a second molecule of reagent may attack the carbonyl group of the ketone, leading to the formation of a tertiary alcohol.

Diketones.—In the case of diketones, both carbonyl groups are attacked by the reagent, with the formation of a di-tertiary alcohol.

Unsaturated Ketones.—When a ketone contains an ethylenic linkage conjugated * with the carbonyl radicle, it is found that the action of the Grignard reagent simultaneously takes two courses. In the first course, a tertiary alcohol is produced by the normal action of the reagent upon the carbonyl group:

$$R\,.\,CH:CH\,.\,CO\,.\,R' \xrightarrow{CH_3\,.\,Mg\,.\,Br} R\,.\,CH:CH\,.\,\overset{\overset{\displaystyle CH_3}{|}}{C}(OH)\,.\,R'$$

The alternative reaction involves both the carbonyl group and the ethylenic bond, the fragments of the Grignard reagent attaching themselves to the extreme ends of the conjugated system —CH : CH . C : O— in the following manner:

* See Chapter III.

$$R.CH:CH.CO.R' + CH_3.Mg.Br$$
$$= R.CH(CH_3).CH:CR'.O.Mg.Br$$
$$R.CH.(CH_3).CH:CR'.O.Mg.Br + H_2O$$
$$= RC.H(CH_3).CH:CR'.OH + HO.Mg.Br$$
$$R.CH(CH_3).CH:CR'.OH = R.CH(CH_3).CH_2.CO.R'$$

Thus the final result of the reactions is the production of a mixture of a tertiary alcohol and a saturated ketone.

Esters of Substituted Acids.—When the carbonyl group forms part of an ester radicle, —COOEt, the reactions in some cases take a slightly different course from the foregoing ones.

Halogen-substituted esters behave towards the Grignard reagent like normal esters, the halogen atom being untouched and the product being simply a halogen-substituted tertiary alcohol:

$$Cl.CH_2.COOEt \xrightarrow{CH_3.Mg.Br} Cl.CH_2.\overset{\displaystyle CH_3}{\overset{|}{C}}(OH).CH_3$$

On the other hand, amino-esters like glycocoll are first attacked at the amino-radicle, and it is only in a later stage of the action with excess of the Grignard reagent that an amino-tertiary alcohol is formed:

$$NH_2.CH_2.COOEt \xrightarrow{CH_3.Mg.Br} NH_2.CH_2.\overset{\displaystyle CH_3}{\overset{|}{C}}(OH).CH_3$$

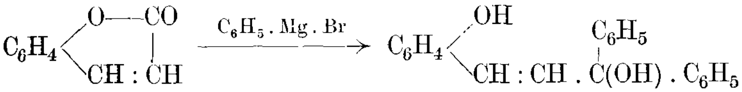
Parallel to this is the case of the hydroxy-esters. Here the hydroxy-group first comes into action, liberating one molecule of the hydrocarbon corresponding to the Grignard radicle. The hydroxy-group being thus masked, any further Grignard reagent will attack the ester group and yield a tertiary alcohol, so that a pinacone is the final product of the action:

$$CH_3.CH(OH).COOEt \xrightarrow{CH_3.Mg.Br} CH_3.CH(OH).\overset{\displaystyle CH_3}{\overset{|}{C}}(OH).CH_3$$

Naturally in cases such as these the end-product's constitution will depend upon the likelihood of dehydration-reactions occurring after the Grignard reagent has done its work; and these dehydrations are specially noticeable in the case of the action of the reagent upon the esters of phenolic acids.

Lactones.—It may be pointed out that lactones generally behave like hydroxy-esters when they are treated with Grignard's

reagent. Coumarin, for example, yields diphenyl-cumaryl alcohol when acted on by phenyl magnesium bromide—



Ketonic Esters.—In the case of ketonic esters, the results depend on the manner in which the Grignard reagent is allowed to act. By choosing the right reaction-conditions it is possible to attack the ketonic carbonyl group while leaving the —COOEt group intact, so that a hydroxy-ester can be formed. Thus isoamyl pyruvate, $CH_3 . CO . COOC_5H_{11}$, yields with methyl magnesium iodide the isoamyl ester of hydroxy-butyric acid: $(CH_3)_2C(OH) . COOC_5H_{11}$.

Some of the ketonic esters, however, behave in a wholly abnormal manner. Equimolecular quantities of acetoacetic ester and methyl magnesium iodide simply regenerate the acetoacetic ester, after treatment with water. This behaviour is easily explicable, since it has been proved that acetoacetic ester is mainly of the enolic structure :

$$CH_3 . C(OH) : CH . COOEt$$

so that the hydroxyl group is simply showing its normal character. Much less easy to explain is the case of the diethyl derivative : $CH_3 . CO . C(Et)_2 . COOEt$. Inspection of its formula will show that it cannot form an enolic variety like the parent substance. When treated with an equimolecular quantity of methyl magnesium iodide, it regenerates some unchanged ester accompanied by about 25 per cent. of *methyl* diethyl-acetate, $(C_2H_5)_2CH . COOCH_3$. On the other hand, when three molecules of the Grignard reagent are mixed with one molecule of ethyl diethyl-acetate, almost the whole of the ester can be recovered unchanged after the reaction-process has been completed.

Mesoxalic ester, EtOOC . CO . COOEt, also behaves abnormally with Grignard's reagent. The central carbonyl group fails to react at all, despite the fact that it has sufficient residual affinity in it to form a hydrate when the acid is mixed with water. Instead, the reagent attacks the ester radicles and yields two tertiary alcoholic groups : $(CH_3)_2C(OH) . CO . C(OH)(CH_3)_2$.

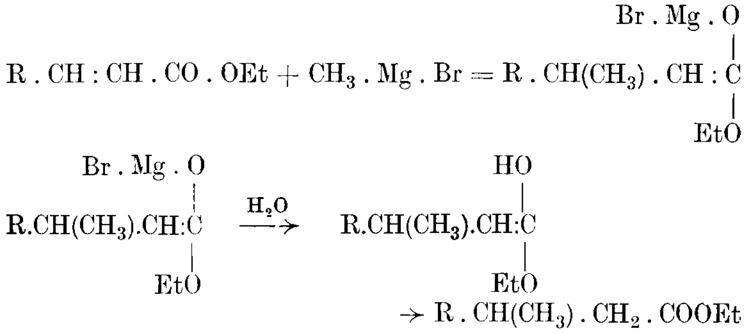
But even at the best, only about 8 per cent. of the mesoxalic ester enters into the reaction.

Esters of Dicarboxylic Acids.—When two ester groups are present in the same molecule, the results of the reaction depend upon the structure of the original ester. Oxalic ester, succinic ester and the higher esters of the same series yield di-tertiary alcohols. Of course, as in the case of the hydroxy-esters, dehydrations of the end-products may occur here also. Malonic ester, on the other hand, reacts first at the methylene group :

$$CH_3 . Mg . Br + CH_2(COOEt)_2 = Br . Mg . CH(COOEt)_2 + CH_4$$

Further application of the Grignard reagent yields as an end-product the usual dihydroxy-derivative of the type: $R_2C(OH) . CH_2 . C(OH)R_2$. In the case of substituted malonic esters, the reaction is rendered further abnormal by the fact that in the majority of cases the reagent attacks only *one* of the ester groups, so that only a single tertiary alcohol radicle is produced instead of two.

Unsaturated Esters.—Unsaturated esters containing an ethylenic linkage in the α-position to the ester group resemble the corresponding unsaturated ketones in their reactions. The Grignard reagent may attack either the carbonyl radicle of the ester group or, alternatively, the two ends of the unsaturated chain. In practice, the latter is the main reaction—



Derivatives of Carbonic Acid.—This survey of the action of the Grignard reagent upon organic compounds may be closed by a reference to the behaviour of the carbonic acid derivatives : carbon dioxide, carbonyl chloride, carbonic ester, and orthocarbonic ester.

In the case of carbon dioxide, there are two double bonds

attached to a single carbon atom; and the action of this gas upon the Grignard reagent can take place in stages :

$$(1)\ CO_2 + CH_3 . Mg . Br = CH_3\text{—}C\begin{smallmatrix} \diagup O . Mg . Br \\ = O \end{smallmatrix}$$

$$(2)\ CH_3\text{—}C\begin{smallmatrix} \diagup O . Mg . Br \\ = O \end{smallmatrix} + CH_3.Mg.Br = CH_3\text{—}C\begin{smallmatrix} \diagup O . Mg . Br \\ \text{—} O . Mg . Br \\ \diagdown CH_3 \end{smallmatrix}$$

Hydrolysis of the magnesium compound formed in (1) yields an acid; hydrolysis of the magnesium derivative formed in stage (2) yields a dihydroxy-compound which splits off water and produces a ketone. In certain cases, these reactions seem to proceed in the Grignard solution spontaneously; and in the final product some tertiary alcohol is detected which has arisen from the action of yet a third molecule of the Grignard reagent upon the ketone produced by stage (2).

$$CH_3\text{—}C\begin{smallmatrix} \diagup O . Mg . Br \\ \text{—} O . Mg . Br \\ \diagdown CH_3 \end{smallmatrix} = CH_3\text{—}C\begin{smallmatrix} = O \\ \diagdown CH_3 \end{smallmatrix} + O(Mg . Br)_2$$

$$CH_3.CO.CH_3 + CH_3.Mg.Br = CH_3\text{–}C\begin{smallmatrix} \diagup CH_3 \\ \text{—} O.Mg.Br \\ \diagdown CH_3 \end{smallmatrix} \xrightarrow{H_2O} CH_3\text{–}C\begin{smallmatrix} \diagup CH_3 \\ \text{—} OH \\ \diagdown CH_3 \end{smallmatrix}$$

When the reaction is carried out at low temperatures, the second stage (and hence the third stage also) is largely inhibited, so that the main product of the reaction is a carboxylic acid. This modification of the process is best attained by dropping solid carbon dioxide into the Grignard reagent.

Carbonyl chloride contains three reactive groups attached to its carbon atom; and when it is made to react with the Grignard reagent, the two chlorine atoms are replaced by alkyl radicles, whilst the carbonyl group behaves as usual; so the end-product is a tertiary alcohol.

With carbonic esters, the Grignard reagent yields esters of fatty acids :

$$EtO.CO.OEt + CH_3.Mg.Br = EtO\text{—}\underset{\displaystyle CH_3}{\overset{\displaystyle O . Mg . Br}{\underset{|}{\overset{|}{C}}}}\text{—}OEt \xrightarrow{H_2O} \begin{matrix} CH_3.COOEt \\ + HO.Mg.Br + EtOH \end{matrix}$$

The action of the Grignard reagent upon orthocarbonic ester is a step-by-step replacement of the ethoxy-groups by alkyl radicles, so that the results can be represented by the following scheme :

$$C(OEt)_4 \rightarrow RC(OEt)_3 \rightarrow R_2C(OEt)_2 \rightarrow R_3C \,.\, OEt$$

3. *The Grignard Reagent and Inorganic Materials*

The use of the Grignard reagent is not confined to its action upon carbon compounds, for its application to many inorganic chemicals has led to results of considerable interest. Some of the reactions of this type will be briefly surveyed in the present section ; and in order to bring the rather disconnected facts into a semblance of order, it will be best to take up in turn the different Groups of the Periodic Table.

Group I.—None of the metals of this group has any influence upon the Grignard reagent ; nor have the halides of the alkalies any action. The chlorides of members of Group I*b*, however, affect the reagent, with results which vary from element to element. Cuprous chloride appears to yield alkyl derivatives of monovalent copper.[1] Cupric chloride reacts according to the following scheme, with the production of hydrocarbons : [2]

$$2R \,.\, Mg \,.\, Br + 2CuCl_2 = R{-}R + 2Cl \,.\, Mg \,.\, Br + Cu_2Cl_2$$

The action of phenyl magnesium bromide on silver chloride or silver bromide yields, among other things, some phenyl-silver, $C_6H_5 \,.\, Ag$, an extremely unstable material which easily explodes when dry.[3] Auric chloride [4] yields a hydrocarbon, metallic gold being precipitated. Some dialkyl auri-halide is formed also ; but the main reaction is as follows :

$$2AuCl_3 + 6R \,.\, Mg \,.\, Br = 2Au + 6Br \,.\, Mg \,.\, Cl + R{-}R$$

Group II.—The chlorides of beryllium,[5] zinc,[6] cadmium,[7] and mercury [8] all interact with the Grignard reagent yielding dialkyl

[1] Reich, *Compt. rend.*, 1923, **177**, 322.
[2] Sakellarios and Kyrimis, *Ber.*, 1924, **57**, 322.
[3] Reich, *Compt. rend.*, 1923, **177**, 322.
[4] Pope and Gibson, *J.*, 1907, **91**, 2061.
[5] Krause and Wendt, *Ber.*, 1923, **56**, 466.
[6] Blaise, *Bull. soc. chim.*, 1911, [4] **9**, 1 ; Job and Reich, *ibid.*, **33**, **1428.**
[7] Krause, *Ber.*, 1917, **50**, 1813.
[8] Marvell and Gould, *J. Amer. Chem. Soc.*, 1922, **44**, 153.

metallic derivatives, the formation of which is preceded, apparently, by the production of mono-alkyl metallic halides, as shown in the equations below:

$$CH_3 . Mg . Br + HgCl_2 = CH_3 . Hg . Cl + Cl . Mg . Br$$
$$CH_3 . Mg . Br + CH_3 . Hg . Cl = CH_3 . Hg . CH_3 + Cl . Mg . Br$$

Group III.—The chlorides of boron,[1] aluminium,[2] and thallium[3] attack the Grignard reagent; but as might be expected from the characters of the elements, the results differ from case to case. Boron fluoride (and apparently the chloride also) can be made to yield derivatives of the following types: $R.BF_2$, R_2BF, R_3B, and $R.B(OH)_2$. Aluminium chloride, on the other hand, yields double compounds of ether and an aluminium trialkyl derivative, such as: $(4AlR_3+3R_2O)$. Thallic chloride yields dialkyl thallic halides, $R_2Tl.Cl$; whilst thallous chloride seems to resemble gold chloride inasmuch as metallic thallium is precipitated during the reaction, though no alkyl derivative is formed.

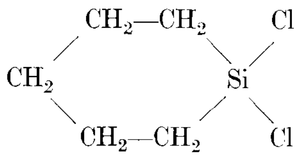
Group IV.—Silicon chloride[4] yields a series of derivatives of the following types, according to the conditions of the reaction: $R.SiCl_3$, $R_2.Si.Cl_2$, $R_3.Si.Cl$ and R_4Si. Stannous chloride[5] yields dialkyl tin derivatives. An interesting case[6] is that of the action of phenyl magnesium bromide on stannous chloride, which yields tin diphenyl, $(C_6H_5)_2Sn$. When this compound is heated with a large excess of phenyl magnesium bromide, it yields hexaphenyl-distannane: $(C_6H_5)_3Sn—Sn(C_6H_5)_3$, the stannic parallel to the parent substance of triphenylmethyl, like which it gives coloured solutions. Stannic chloride resembles silicon tetrachloride in its action, the result being a step-by-step replacement of chlorine atoms by alkyl groups. Lead chloride, when subjected to the action of the Grignard reagent, also shows a somewhat surprising change in valency, as the reaction[7] takes the following course:

$$4R . Mg . Br + 2PbCl_2 = PbR_4 + Pb + 4Cl . Mg . Br$$

[1] Strecker, *Ber.*, 1910, **43**, 1131; Krause and Nitsche, *ibid.*, 1921, **54**, 2784.
[2] Krause and Wendt, *Ber.*, 1923, **56**, 466.
[3] Meyer and Bertheim, *Ber.*, 1904, **37**, 2501; Goddard, *J.*, 1921, **119**, 672; 1922, **121**, 256.
[4] Bygdén, *Ber.*, 1911, **44**, 2640.
[5] Pfeiffer, *Ber.*, 1911, **44**, 1269.
[6] Krause and Becker, *Ber.*, 1920, **53**, 173.
[7] Pfeiffer and Truskier, *Ber.*, 1904, **37**, 1125.

In addition to the tetra-alkyl derivatives, the diaryl and triaryl series can also be obtained.[1]

Silicon, lead, and tin are distinguished by their capacity for forming cyclic compounds under the action of the Grignard reagent. When silicon chloride acts on a Grignard reagent prepared from 1, 5-dibromopentane and having the following constitution: $Br . Mg . CH_2 . CH_2 . CH_2 . CH_2 . CH_2 . Mg . Br$, the result is a compound of the formula:



wherein the two chlorine atoms can be replaced by methyl groups on further treatment with methyl magnesium bromide. An exactly analogous lead compound is obtained by the action of diethyl lead dichloride upon the same Grignard reagent derived from 1, 5-dibromopentane.[2] Similar results are obtained with diethyl-tin dibromide.[3]

Group V.—Ammonia's action has already been described in the previous section of this chapter. Nitrous oxide has no effect on the Grignard reagent; but from nitric oxide,[4] nitroso-hydroxylamine derivatives are obtained:

$$C_6H_5 . Mg . Br + 2NO = C_6H_5\text{—}\underset{\displaystyle O . Mg . Br}{\underset{|}{N}}\text{—}N : O \longrightarrow C_6H_5\text{—}\underset{\displaystyle OH}{\underset{|}{N}}\text{—}N : O$$

Nitrogen peroxide[5] is reduced and alkylated by the Grignard reagent, the end-product being a $\beta\beta$-dialkylated hydroxylamine. The action of nitrosyl chloride upon phenyl magnesium bromide forms a simple method of obtaining nitrosobenzene:

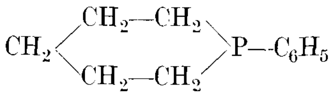
$$C_6H_5 . Mg . Br \quad + \quad NOCl \quad = \quad C_6H_5 . N : O \quad + \quad Cl . Mg . Br$$

Phosphorus,[6] arsenic,[7] antimony,[7] and bismuth[8] chlorides all

[1] Krause and others, *Ber.*, 1919, **52**, 2165; 1921, **54**, 2060; 1922, **55**, 888.
[2] Bygdén, *Ber.*, 1915, **48**, 1236; Grüttner and Krause, *Ber.*, 1917, **50**, 574.
[3] Grüttner, Krause, and Wiernik, *Ber.*, 1917, **50**, 1549.
[4] Sand and Singer, *Annalen*, 1903, **329**, 190.
[5] Wieland, *Ber.*, 1903, **36**, 2315.
[6] Auger and Billy, *Compt. rend.*, 1904, **139**, 597.
[7] Hibbert, *Ber.*, 1906, **39**, 160.
[8] Pfeiffer, *Ber.*, 1904, **37**, 4620.

yield trialkyl derivatives of the element employed in the Grignard reaction. Mono- and di-alkyl derivatives are also obtainable.

It is of some interest to note that by means of the Grignard reagent it is possible to prepare the analogue of an N-alkyl substituted piperidine corresponding to each of the remaining elements of Group V*a*. In each case the Grignard reagent is prepared from 1,5-dibromopentane and is allowed to act upon phosphenyl chloride, $(C_6H_5)PCl_2$, phenyl-dichloro-arsine, $(C_6H_5)AsCl_2$, phenyl-dichloro-stibine, $(C_6H_5)SbCl_2$, or ethyl-bismuth dichloride, $(C_2H_5)BiCl_2$, according to the end-product required. In this way cyclopentamethylene-phenylphosphine



and its analogues can be obtained, and several fresh examples of heterocyclic groupings have thus been shown to exist.

Group VI.—Oxygen is the first element we encounter which has the power of attacking the Grignard reagent. The action which might be expected would be as follows :

$$2R . Mg . Br \quad + \quad O_2 \quad = \quad 2R . O . Mg . Br$$

In practice, however, the reaction is much complicated by side-reactions and very little practical importance attaches to it. In the case of sulphur,[1] the secondary reactions are not so marked, and quite good yields of mercaptans can be obtained :

$$R . Mg . Br + S = R . S . Mg . Br \xrightarrow{H_2O} RSH + HO . Mg . Br$$

When excess of sulphur is present, the intermediate product, R . S . Mg . Br, reacts with an extra atom of sulphur and yields a disulphide—

$$2R . S . Mg . Br \quad + \quad S \quad = \quad R . S . S . R \quad + \quad S(MgBr)_2$$

Selenophenol [2] and tellurophenol [3] can be obtained from the elements and the Grignard reagent in a manner exactly analogous to the preparation of thiophenol.

The chlorides of sulphur give complicated reactions with the Grignard reagent ; selenium dichloride also shows a divergence

[1] Wuyts, *Bull. soc. chim.*, 1909, [4], **5**, 405.
[2] Wuyts, *Bull. soc. chim.*, 1909, [4], **5**, 405.
[3] Giua and Cherchi, *Gazzetta*, 1920, **50**, i. 362.

from the expected results. Tellurium dichloride yields diphenyl telluride with phenyl magnesium bromide.

Sulphur dioxide [1] acts analogously to carbon dioxide, the product of the reaction being the magnesium derivative of an alkyl-sulphinic acid: $R.SO_2.Mg.Br$. As might be anticipated from this, thionyl chloride [2] offers a complete parallel to carbonyl chloride, yielding first the compound, R . SO . R and then, by further action of the reagent on the —SO— group, the compound $R_3S.O.Mg.Br$. When an aliphatic Grignard reagent acts upon excess of sulphuryl chloride, about 30 per cent. of sulphone is formed; but when an aromatic Grignard reagent is employed, a sulphonic acid is the main product and only a minor quantity of sulphone is formed.[3]

Chromium is the only element of Group VI*a* which has a chloride capable of reacting with the Grignard reagent. The main reaction is supposed [4] to take the following course:

$$5C_6H_5.Mg.Br + 4CrCl_3 = (C_6H_5)_5Cr.Br + 2MgBr_2 + 3MgCl_2 + 3CrCl_2$$

On treatment with caustic potash, this pentaphenyl chromium chloride yields the corresponding hydroxide: $(C_6H_5)_5Cr.OH$ which is remarkable on account of the fact that when treated with acids it ejects a phenyl radicle and yields salts like: $(C_6H_5)_4Cr.Br$.

Group VII.—The normal action of halogens upon the Grignard reagent should be a simple replacement of the alkyl group by a halogen atom with the accompanying formation of alkyl halide. In practice, however, the yields seem to depend upon the nature of the halogen involved and the reaction-conditions.[5]

Group VIII.—Platinum chloride [6] reacts the Grignard in the following manner:

$$3CH_3.Mg.I + PtCl_4 = (CH_3)_3Pt.I + 2MgCl_2 + MgI_2$$

No other member of the eighth Group appears capable of attacking the Grignard reagent, which is somewhat surprising in view of the analogies between iron and aluminium.

[1] Rosenhain and Singer, *Ber.*, 1904, **37**, 2152.
[2] Grignard and Zorn, *Compt. rend.*, 1910, **150**, 1177.
[3] Cherbuliez and Schnauder, *Helv. Chim. Acta*, 1923, **6**, 249.
[4] Hein, *Ber.*, 1919, **52**, 195; 1921, **54**, 1905, 2708, 2727; 1924, **57**, 8.
[5] Datta and Mitter, *J. Amer. Chem. Soc.*, 1919, **41**, 287.
[6] Pope and Peachey, *J.*, 1909, **95**, 571.

4. *The Formation and Properties of Ozonides* [1]

The foregoing pages are sufficient to show how multifarious are the applications of Grignard's discovery ; and it is not to be expected that the other new reagents of organic chemistry will show such wide adaptability. The next to be dealt with here is ozone, which has a comparatively restricted field of application.

When ozone acts upon compounds containing ethylenic or acetylenic linkages, one bond is ruptured and three oxygen atoms attach themselves to the molecule in the following way : [2]

$$\begin{matrix} R_2C \\ \| \\ R_2C \end{matrix} + O_3 = \begin{matrix} R_2C \\ | \\ R_2C \end{matrix}\!\!>\!O_3 \qquad \begin{matrix} R{-}C \\ ||| \\ R{-}C \end{matrix} + O_3 = \begin{matrix} R{-}C \\ \| \\ R{-}C \end{matrix}\!\!>\!O_3$$

The fact that the double ethylenic bond is saturated by the addition of the ozone molecule is established, since the resulting ozonide does not decolorize a solution of bromine in acetic acid.

The rapidity with which ozone acts upon ethylenic derivatives is influenced by constitutional factors ; for ordinary ethylenic compounds are rapidly attacked, whereas when ozone reacts with substances containing conjugated double bonds, the two unsaturated groups are influenced in turn instead of being simultaneously affected. The action of ozone upon polynuclear hydrocarbons like naphthalene resembles the mode of attack of reducing agents, since one ring is completely saturated before the second ring is affected. The presence of substituents has also an influence in the case of aromatic derivatives. For example, aniline undergoes a normal oxidation process before the formation of an ozonide takes place at all.

Ozonization is usually carried out in a solution, the solvent chosen being one which is itself unaffected by ozone, such as saturated hydrocarbons or simple alkyl halides. After the

[1] The details of the ozone technique are given in Houben-Weyl's *Methoden der organischen Chemie*, which contains very full references. The papers of Harries have been reprinted under the title *Untersuchungen über das Ozon.* A general conspectus of work done in this field up to 1915 is given in Fonrobert's *Das Ozon.*

[2] For some views as to the mode of action of the ozone molecules, see Engler and others, *Ber.*, 1897, **30**, 1669 ; 1899, **31**, 3046 ; 1900, **33**, 1090, 1097, 1109 ; 1901, **34**, 2933 ; Klages and Heilmann, *Ber.*, 1904, **57**, 1449 ; Tiffeneau, *Bull. Soc. chim.*, 1902, [iii] **27**, 1066 ; Wallach, *Annalen*, 1905, **343**, 28.

process is complete, the solvent is removed by evaporation, leaving the ozonide behind.

The physical character of the ozonides varies according to the compounds from which they are obtained. Some are oils or syrups; others are glassy bodies; whilst a few can be obtained in crystalline form. Some of them are volatile; but many of them cannot be distilled in vacuo at ordinary temperatures; and as they are all extremely unstable and most of them are highly explosive, the difficulty of purifying them is considerable. The majority of them are soluble in all the normal organic solvents except ligroin; but though some of them are slightly soluble in water, this solvent cannot be utilized, since it exerts a decomposing action upon the ozonides as a class.

The molecular weights of ozonides have been determined by the usual methods, and in most cases they are found to be normal. Dimeric forms of the ozonides of ethylene [1] and butylene,[2] have been detected in addition to the normal monomolecular types.

The ozonides decolorize permanganate solution and discharge iodine from potassium iodide. They oxidize solutions of indigo. Concentrated sulphuric acid decomposes them with charring and often explosively.

5. *Ozone as a Reagent in Constitution Determination*

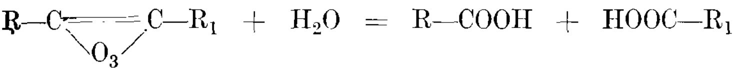
The chief value of the ozonides lies in their break-up into simpler materials, a decomposition which may occur either under the influence of water or else in anhydrous solvents. The ozonide molecule splits at the position of the original ethylenic bond; and by identifying the fragments thus formed, it is possible to gain an insight into the constitution of the initial molecule upon which the ozone acted. Usually hydrogen peroxide is liberated during the decomposition of the ozonides by water; but curiously enough this has not been detected in the cases of ozonides derived from acetylenic bodies or from benzene and its homologues. The readiness with which the ozonides undergo this decomposition varies from compound to compound: the ozonides of hydroaromatic substances are generally fairly stable, whereas ozonides of compounds containing oxygen (such as

[1] Harries and Kötschau, *Ber.*, 1909, **42**, 3305.

[2] Harries and Evers, *Ber.*, 1912, **45**, 936.

unsaturated ketones) are often decomposed with dangerous rapidity.

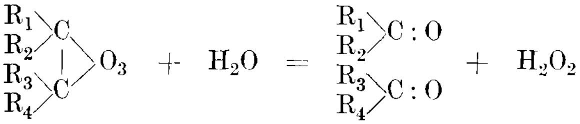
The simplest decomposition is that undergone by ozonides derived from acetylenic compounds, for in this case two acid molecules are liberated :



Obviously the identification of the two acids will give the key to the position of the triple bond in the original molecule.

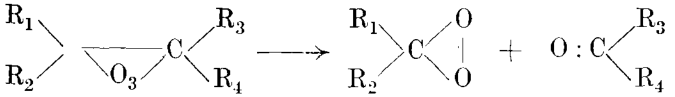
In the case of ozonides derived from ethylenic compounds, the possible decompositions are much more complex. It will be best to take them one by one.

The simplest case is that in which two ketonic or aldehydic molecules are produced in the following manner :



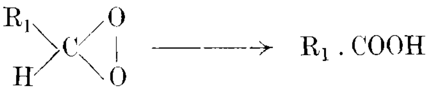
The identification of the two ketones gives a clue to the constitution of the original ethylenic derivative.

In the second type of decomposition, water does not enter into the reaction, and the products are mixtures of a ketone and a ketonic peroxide :



Of course in this case the peroxide $R_3 . CO_2 . R_4$ and the ketone $R_1 . CO . R_2$ may also be formed, so that there are four reaction products to disentangle, instead of only two.

When one of the groups R is a hydrogen atom, a further change in the peroxide may be expected :



It is obvious from the foregoing that in practice the ozone method is by no means so simple as might appear at first sight ; and that difficulty in its application may arise from the complexity of the reaction-products which it yields.

When glacial acetic acid is substituted for water as a decomposing-material for ozonides, the method employed is the same, but the break-down of the ozonides is usually easier than when water is employed. On the other hand, when glacial acetic acid is used, all the possible decomposition products seem to be formed, which may or may not be advantageous.

Enough has now been said to indicate the application of ozone in the determination of the position of ethylenic and acetylenic bonds in molecules. One or two examples may be given here of other problems to which ozone has furnished a key.

In some cases ethylenic compounds exist in two different forms which might be assumed to be either structural isomers or stereoisomers; and the difficulty of breaking up their chains in conditions and by reagents which exclude the possibility of isomeric change is a matter which puts difficulty in the way of settling the question in favour of one or other form of isomerism. It has been shown [1] that when two stereoisomeric acids, such as oleic and brassidic acid, are acted on by ozone, they not only yield the same decomposition products but the relative yields of the decomposition products are identical in the two cases. Since under the conditions of ozonization no alteration in constitution is to be expected, this method offers marked advantages in an attempt to prove that two compounds are stereoisomeric.

In the investigation of polynuclear hydrocarbons, the ozone method allows the complete removal of one of the rings; and in this case also the fact that the reaction takes place at ordinary temperatures is of value.

The application of the ozone method to the case of dynamic isomerides [2] has furnished a fresh mode of investigation in the field of keto-enolic change. By determining the point of attack of the ozone, at low temperatures which preclude rapid change in the equilibrium between the ketonic and enolic forms, much valuable information may be gained as to the constitution of the material under examination, and some evidence as to the relative quantities of the two forms present may also be gathered.

[1] Harries and Thieme, *Ber.*, 1906, **39**, 2844.
[2] Scheiber and Herold, *Ber.*, 1914, **47**, 2704.

6. *Oxidation by Means of Ozone*

In addition to ethylenic and acetylenic derivatives, ozone has the power of attacking many oxygen compounds. Thus methyl alcohol yields formaldehyde.[1] Ethyl alcohol[2] does not behave similarly, however, for instead of acetaldehyde it produces an ethyl hydroperoxide which is different from that obtained by Baeyer and Villiger.[3] Since the structure of the last-named material is believed to be C_2H_5—O—O—H, the hydroperoxide produced by ozone has been given the formula :

$$\begin{array}{l} C_2H_5\text{—}\overset{}{O}:O \\ \qquad\;\;\; | \\ \qquad\;\;\; H \end{array}$$

Ozone oxidizes glycerine[4] to glycerine aldehyde, dulcite[5] to galactose, and mannite[5] to glucose and fructose. Ether[6] yields a peroxide-like substance, but the explosive character of this product has made thorough investigation of it impossible.

As a general rule, aldehydes and ketones can be made to take up one molecule of oxygen, which attaches itself to the oxygen atom already present in the molecule. The result is the formation of peroxides which resemble the ozonides in character to some extent. These peroxides formed by the action of ozone on aldehydes and ketones are not necessarily identical with the peroxides obtained by the break-up of ozonides. For example, Harries[7] prepared two forms of nonyl-aldehyde peroxide, $C_8H_{17}.CHO_2$: one by ozonization of nonyl aldehyde, the other by the break-up of the ozonide of oleic acid. It is assumed that ozonization of aldehydes leads to compounds of the structure (I.) whilst the decomposition of ozonides produces substances having the structure (II.).

$$\text{(I.) } R.CH:O:O \qquad \text{(II.) } R.CH\!\left\langle\begin{array}{l} O \\ | \\ O \end{array}\right. \qquad \text{(III.) } R.\overset{OH}{\overset{/}{C}}:O:O$$

[1] Harries, *Ber.*, 1903, **36**, 1933.
[2] Harries, *Ber.*, 1903, **36**, 3658.
[3] Baeyer and Villiger, *Ber.*, 1900, **33**, 3387.
[4] Harries, *Ber.*, 1903, **36**, 1933.
[5] Harries and Langheld, *Z. physiol. Chem.*, 1903, **51**, 373.
[6] Harries and Weiss, *Annalen*, 1905, **343**, 311.
[7] Harries, *Annalen*, 1910, **374**, 288.

The lower fatty acids yield no peroxides at the carboxyl group; but some fatty acids of high molecular weight, such as oleic acid, appear to form peroxides of the type (III.). Acid amides, although they contain a carbonyl group, do not seem to yield any peroxides.

Compounds of the aromatic series undergo drastic changes under the action of ozone. Thus benzene behaves as if it contained three normal ethylene bonds; for it takes up three molecules of ozone, yielding a triozonide which breaks down with water to give three molecules of glyoxal. Although aliphatic amines are unaffected by ozone, aniline and aromatic amino-acids are profoundly altered. In the case of iodobenzene,[1] the action of ozone is directed first to the iodine atom; and iodosobenzene, $C_6H_5 . I : O$, is produced. Phenylacetic acid,[2] on the contrary, is apparently attacked at the nucleus, since only traces of benzoic acid are to be found among the reaction products after 80 per cent. of the original substance has been broken down.

7. *Some Modern Methods of Alkylation*

It is often necessary to replace the hydrogen atoms of hydroxyl or amino-groups by alkyl radicles; and in recent times a number of new methods have been discovered which lead to this result. The more interesting of these will be briefly described in the present section. It is unnecessary to deal with older methods, such as the action of alkyl halides upon sodium alcoholates or phenolates, the replacement of the group $—N:N.OH$ by $—OEt$ by the diazo-reaction, alkylation by means of silver oxide and alkyl iodides, etc., since these are described in the ordinary text-books.

Diazomethane.—One of the most effective methylating agents is diazomethane, which acts on phenols in the following manner:

$$C_6H_5.OH + CH_2N_2 = C_6H_5.O.CH_3 + N_2$$

Methylation of the amino- and imino-groups is also possible in some cases; for example, phthalimide and diazomethane yield N-methyl-phthalimide. The advantages of diazomethane as a reagent are twofold: it gives almost quantitative yields; and

[1] Harries, *Ber.*, 1903, **36**, 2998.
[2] Rupe and Iselin, *Ber.*, 1916, **49**, 25.

it acts at ordinary temperatures, thus minimizing possible intramolecular changes. Its grave disadvantage is its poisonous character.

Dimethyl sulphate.—Dimethyl sulphate, $(CH_3)_2SO_4$, is a methylating agent which has found even wider application. Its action upon phenols takes place in two stages, the first of which is complete at ordinary temperatures, whilst the second stage is slower and requires a higher temperature for its completion:

$$C_6H_5 . O . Na + CH_3O . SO_2 . OCH_3 . = C_6H_5 . O . CH_3 + NaO . SO_2 . OCH_3$$
$$C_6H_5 . O . Na + NaO . SO_2 . OCH_3 = C_6H_5 . O . CH_3 + Na_2SO_4$$

The application of dimethyl sulphate in the methylation of the carbohydrates [1] has proved to be one of the great practical advances in this field, since it renders the preparation of methylated sugars and glucosides easy, under conditions which avert changes of constitution in these sensitive materials. Dimethyl sulphate has also been applied with success to the methylation of amines, since either one or two methyl groups can be introduced, according to whether one or two molecules of dimethyl sulphate are employed.

Dimethyl sulphate has the following advantages as a reagent: It is cheap when compared with methyl iodide; it reacts almost instantaneously in the first of the foregoing stages; it gives almost quantitative yields; and, finally, its high boiling-point (188° C.) permits methylation in flasks without the use of the bomb-furnace or sealed tubes. Like diazomethane, however, it has the drawback of being very poisonous.

In the second equation showing the action of dimethyl sulphate, it will be noticed that the real reagent is sodium methyl sulphate; and this suggests that salts of monoalkyl sulphates have an application in alkylation. In practice, however, their field of employment is limited, since their action demands the e of higher temperatures, as has already been noted. In neral, alkylation by their help is carried out under pressure, hich makes them much less convenient than dimethyl sulphate.

Aryl sulphonic esters, such as *p*-toluene-sulphonic ester, ve been found to be alkylating agents of great value, as they

[1] Denham and Woodhouse, *J.*, 1913, **103**, 1735; Haworth, *J.*, 1915, **107**, 8.

are applicable even in the case of compounds difficult to alkylate by ordinary methods. The reaction takes the following course :

$$C_6H_5.O.Na + C_6H_5.SO_2.OCH_3 = C_6H_5.O.CH_3 + C_6H_5.SO_3Na$$

These esters are applicable also in the methylation of amines.

Chloroformic Ester.—Two more specialized reagents may be given a place here. When chloroformic esters act on phenols in pyridine solution, mixed carbonic esters are formed ; and these, on heating, give off carbon dioxide and leave phenol ethers :

$$C_6H_5 . OH + Cl . COOCH_3 = C_6H_5 . O . CO . O . CH_3 + HCl$$
$$C_6H_5 . O . CO . O . CH_3 = C_6H_5 . O . CH_3 + CO_2$$

This reaction cannot, of course, be applied to the amines, since the group —NH . COOR which would be formed in that reaction is not easily broken up.

Formaldehyde.—Formaldehyde can act as a methylating agent for amines in certain cases. The reaction takes place in two stages, the first of which is the formation of an addition-product of aldehyde and amine, whilst the second stage is the reduction of this compound by excess of formaldehyde :

$$R . NH_2 \xrightarrow{HCHO} H_2C(OH) . NH . R \xrightarrow{HCHO} CH_3 . NH . R$$

The method is considerably restricted, however, owing to the likelihood of other reactions between the aldehyde and amine occurring simultaneously and even preponderantly. Sometimes these can be avoided by the addition of formic acid to the reagents.[1]

Catalytic Methods.—Some catalytic methods of alkylation remain to be mentioned. When a mixture of alcohols, or of a phenol and an alcohol, is passed over heated thorium oxide,[2] ethers are formed ; and the latter method has been found to work well in the case of phenols. Aluminium oxide acts as a high-temperature catalyst in the methylation of aryl amines by means of methyl alcohol,[3] and aluminium alcoholates [4] are

[1] Hess and others, *Ber.*, 1918, **50**, 344, 351.
[2] Sabatier and Mailhe, *Compt. rend.*, 1910, **151**, 359.
[3] Mailhe and Godon, *Compt. rend.*, 1918, **166**, 467, 564.
[4] Lazier and Adkins, *J. Amer. Chem. Soc.*, 1924, **46**, 741.

also serviceable. Calcium chloride, zinc chloride, copper powder, and cupric chloride have been used with success.

8. *Sodamide*

The normal method of introducing an amino-group into a molecule, by nitration and subsequent reduction, is rather cumbrous; and as the amino-radicle is so important in organic chemistry, it is interesting to find a fresh reagent which permits of the direct insertion of the amino-group. This reagent sodamide, which is prepared by passing dry ammonia gas ov sodium heated to 400° C.

When sodamide is allowed to act upon alkyl halides [1] di solved in liquid ammonia at —40° C., the main products a primary amines; though there is a secondary reaction whic yields olefinic hydrocarbons:

$$C_2H_5Br + NaNH_2 = C_2H_5 . NH_2 + NaBr$$
$$C_2H_5Br + NaNH_2 = C_2H_4 + NH_3 + NaBr$$

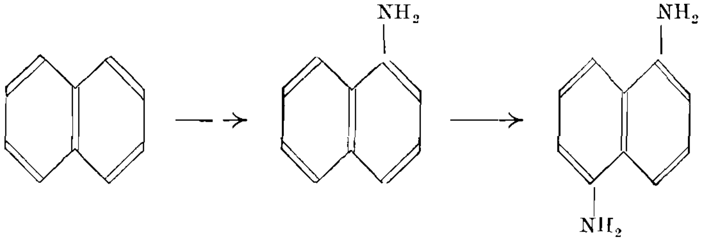
In the aromatic series also, sodamide has proved itse a useful agent. When benzene sulphonic acid is fused wit sodamide, it yields aniline, just as phenol is produced b fusing the sulphonic acid with sodium hydroxide:

$$C_6H_5\text{—}SO_3H + NaNH_2 = C_6H_5\text{—}NH_2 + NaHSO_3$$

The yield in this particular case, however, is only about 10 p cent. When the same reaction is applied to the naphthol su phonic acids, the sulphonic groups are exchanged for amin radicles; but here the yields are over 50 per cent., so that t process is quite a sound one.[2] The reaction has been applie to the anthraquinone derivatives also, with success.[3]

The naphthalene derivatives seem to be most favourab subjects for this method of amino-group insertion; for ev naphthalene itself can be converted into amines by fusing wi phenol and sodamide. The first product is α-napthylamin and by a further action, 1 : 5-naphthalene-diamine is formed:

[1] Chablay, *Compt. rend.*, 1913, **156**, 327.
[2] Jackson and Wing, *Ber.*, 1886, **19**, 902; Sachs, *Ber.*, 1906, **39**, 3009.
[3] Sachs, *Ber.*, 1906, **39**, 3009.



During the reaction, the phenol is reduced to benzene.[1]

By a similar fusion with sodamide, the naphthols can be converted into amino-naphthols having the amino-groups in the 5-position.

The action of the sodamide upon derivatives of pyridine and quinoline has been studied by Tschitschibabin and his collaborators.[2] In this case the reaction is carried out in solutions of toluene, xylene, etc., at 120°–150° C. Hydrogen is evolved; and the amino-group takes the place of the eliminated atoms. Thus from pyridine it is possible to obtain α-aminopyridine.

In one case the action of sodamide is peculiar. When diaryl ketones [3] are treated with sodamide in boiling benzene, toluene, etc., the amide is added on to the ketone :

$$R_2C:O \quad + \quad NaNH_2 \quad = \quad R_2C(ONa).NH_2$$

In presence of water, this compound splits up, yielding a hydrocarbon and an amide :

$$R_2C(ONa).NH_2 + H_2O = R.CO.NH_2 + R.H + NaOH$$

When aryl-alkyl ketones of the type Ar—CO—C(Alk)$_3$ are treated with sodamide and subsequently with water, the products are an aromatic hydrocarbon and an amide of the tri-substituted acetic acid.[4]

$$(CH_3)_3C—CO—C_6H_5 \xrightarrow[+H_2O]{NaNH_2} (CH_3)_3C.CONH_2 + C_6H_6 + NaOH$$

Sodamide has another property which makes it a valuable reagent in certain cases. It has been found to assist the progress of addition and condensation reactions. For example,

[1] Sachs, *Ber.*, 1906, **39**, 3023.

[2] Tschitschibabin and others, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216; 1918, **50**, 519, 534, 543, 548; 1921, **53**, 238; *Ber.*, 1921, **54**, 814.

[3] Haller and Bauer, *Compt. rend.*, 1908, **147**, 824.

[4] Haller and Bauer, *Compt. rend.*, 1908, **147**, 824; 1909, **149**, 5.

Ruzicka[1] allowed acetylene to react upon dihydro-pseudo-ionone in presence of sodamide, whereupon addition took place in the following manner :

$$
\begin{array}{l}
\phantom{C_{10}H_{14}-CH_2-C:O + H.C\equiv C.H = C_{10}H_{14}-CH_2-}C\equiv CH \\
\phantom{C_{10}H_{14}-CH_2-C:O + H.C\equiv C.H = C_{10}H_{14}-CH_2-}| \\
C_{10}H_{14}-CH_2-C:O + H.C\equiv C.H = C_{10}H_{14}-CH_2-C-OH \\
\phantom{C_{10}H_{14}-CH_2-}| \phantom{:O + H.C\equiv C.H = C_{10}H_{14}-CH_2-}| \\
\phantom{C_{10}H_{14}-CH_2-}CH_3 \phantom{+ H.C\equiv C.H = C_{10}H_{14}-CH_2-}CH_3
\end{array}
$$

In the case of the elimination of water between two reacting molecules, it has been found that sodamide has marked advantages over older reagents such as lime water or barium hydrate solution. For example, when citral is condensed with acetone to form pseudo-ionone, it is found that very little sodamide is required to promote the process ; the reaction goes rapidly at ordinary temperatures ; and the yield is 30 per cent. higher than with the other two reagents mentioned above.[2] Sodamide is specially applicable in cases wherein the reaction product is sensitive to the action of water.

Sodamide has also been employed with marked success in those condensations during which alcohol is eliminated. Thus, for example, acetone and acetic ester react in presence of sodamide to yield acetyl-acetone :

$$
\begin{aligned}
&CH_3.CO.OEt + CH_3.CO.CH_3 \\
&\qquad = CH_3.CO.CH_2.CO.CH_3 + EtOH
\end{aligned}
$$

The reaction proceeds much more smoothly in presence of sodamide than it does when sodium or sodium ethylate is used ; and there is no marked production of amide from the ester, which might have been expected.[3] Sodamide has also been employed with success in formic ester condensations which lead to the formation of oxymethylene-ketones.[4]

Mention may also be made of the utilization of this reagent in the phenyl-glycine condensation stage of the indigo synthesis, wherein it has been found of value.

[1] Ruzicka, *Helv. Chim. Acta*, 1923, **6**, 483.
[2] Tiemann, *Ber.*, 1898, **31**, 841.
[3] Bulow and Grotowsky, *Ber.*, 1901, **34**, 1483 ; Claisen and Feyerabend, *Ber.*, 1905, **38**, 695.
[4] Claisen, *Ber.*, 1905, **38**, 696.

CHAPTER III

ADDITION REACTIONS

1. *Introductory*

WHEN two compounds interact with one another there are two possible courses: in the one case from the two original molecules two or more new molecules may be formed; while in the second case the two molecules coalesce to form a single substance. The latter type of interaction is what is understood by the term "addition reaction."

The importance of addition reactions from the point of view of theory has been very widely recognized, as is testified by the flood of hypotheses which have been put forward in this branch at one time or another. We cannot attempt to give a complete sketch of the various views which have been suggested, and must content ourselves with brief accounts of several attempts to formulate the principles underlying the practical side of the subject. The relation between stereochemical influences and the products of addition reactions lies outside the province of the present volume; and attention will be confined to the purely structural side of the question.

There is very little connection between the views which different authors have brought forward to deal with the addition question, and consequently it is difficult to arrange the various theories in anything resembling logical sequence. The simplest arrangement seems to be to begin with the more general views, and deal later with those of more restricted scope.

2. *Michael's Distribution Principle*

The most general view of all has been taken by Michael.[1] According to him, addition is caused by the affinity of the two

[1] Michael, *J. pr. Chem.*, 1888, II. **37**, 524; 1899, **60**, 286, 409; 1903, **68**, 487; *Ber.*, 1906, **39**, 2138.

interacting molecules for each other, and takes place in the manner which produces the most "chemically saturated" compound. But, as he points out, this "neutralization" of affinity depends very largely upon the character of the atoms forming the two interacting molecules. For instance, suppose that the two molecules

A—B   C—D

are capable of reacting together. Let us first consider the affinity of A for C and for D. If the affinity of A for C is greater than that of A for D, then we should expect to find A attaching itself to C, and leaving B to attach itself to D, thus forming the compound—

```
A   B
|   |
C — D
```

But this leaves out of account the attraction of B for C. If this were greater than the attraction of B for D, then we should expect the formation of the compound—

```
B   A
|   |
C — D
```

It is obvious that the actual result of the reaction will depend upon the relative intensity of the forces between A and C and between B and C, coupled with the relative intensity of the forces between A and D and between B and D. Let us represent the forces between A and C by *ac* and those between B and C by *bc*, also those between A and D by *ad* and those between B and D by *bd*. Then the forces which are favouring the formation of the first type—

```
A   B
|   |
C — D
```

(I.)

will be represented by $ac + bd$, while those favouring the formation of—

```
B   A
|   |
C — D
```

(II.)

will be represented by $bc + ad$. The amounts of the two compounds formed during the progress of the reaction will therefore be to one another in the ratio of $ac + bd : bc + ad$. This is termed Michael's *Distribution Principle.*

The consideration of a concrete case will make the matter clearer. Suppose that propylene, $CH_3 . CH : CH_2$, is allowed to react with hydriodic acid. Two possible products may result; for in the one case the iodine atom may attach itself to the middle carbon atom, while in the other it may be attracted by the end carbon atom.

(I.)	(II.)	
$CH_3 . CHI . CH_3$	$CH_3 . CH_2 . CH_2I$	(300 : 1)

It has been found that about three hundred times more of (I.) is formed than (II.). This is due to the great chemical difference between the hydrogen and iodine atoms of hydriodic acid. But if we lessen this difference between the two atoms by substituting a chlorine atom for hydrogen (using iodine chloride instead of hydriodic acid), we find that the iodine atom now attaches itself to the end of the chain rather than to the central atom, the amounts of the compound (I.*a*) and (II.*a*) being formed in the ratio of three to one—

(I.*a*.)	(II.*a*.)	
$CH_3 . CHCl . CH_2I$	$CH_3 . CHI . CH_2Cl$	(3 : 1)

The directing influences at work may be still further neutralized if bromine chloride be used instead of iodine chloride. In this last case there is a great similarity between the two atoms, and, as a result, the two possible end-products are formed in very nearly equal proportions (1·4 : 1)—

(I.*b*.)	(II.*b*.)	
$CH_3 . CHCl . CH_2Br$	$CH_3 . CHBr . CH_2Cl$	(1·4 : 1)

Michael's principle, however, does not go far enough to bring into line all the relevant facts. The addition of hydrobromic acid to a compound of the type $CH_2 : C(CH_3)_2$ results mainly in the production of $CH_3 . CBr(CH_3)_2$, wherein the halogen atom has attached itself to the tertiary carbon atom. It is impossible to dissociate this from the fact that bromination of the compound $CH_3 . CH(CH_3)_2$ leads as a main reaction to the formation of $CH_3 . CBr(CH_3)_2$, wherein the tertiary carbon atom is again attacked. Obviously there is some peculiar quality in the

tertiary grouping which renders it vulnerable ; for the paraffin $CH_3 . CH(CH_3)_2$ is as easily oxidized as an olefine, by means of potassium permanganate.[1] This behaviour of a purely aliphatic compound is sufficient to show that the similar reactivity of the tertiary hydrogen atom in triphenylmethane is not due to the influence of the phenyl radicles in the molecule, but depends upon some much simpler factor. This factor seems of considerable interest in its connection with the *Distribution Principle.*

3. *Vorländer's Hypothesis*

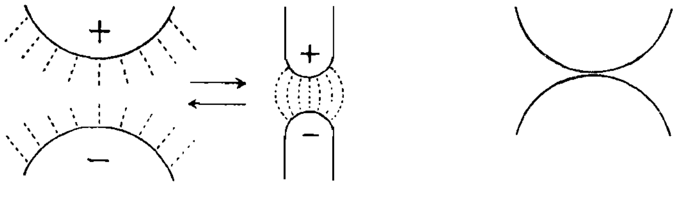
We must now turn to the views of Vorländer.[2] If certain $\alpha\beta$-unsaturated ketones be allowed to react with an acid, the first substances formed are coloured, unstable bodies. This series of bodies Vorländer designated as Type 𝔄. These compounds may undergo a change, being converted into white stable substances which Vorländer classed together under the heading Type 𝔅. According to Vorländer, these two series of substances differ from each other in the following way.

If we regard different states of unsaturation as the outcome of the different capacities of the elements and radicles for positive or negative electricity (of course this is merely used as an analogy), then in the case of the addition of two oppositely charged compounds there are two possibilities—

A. There may be no complete neutralization of the electric charges. In this case the electricity which was originally spread over the surface of the substances becomes concentrated into a comparatively small area by the attraction of the opposite charge on the second substance, and consequently strain is set up.

B. The compounds unite together and become discharged.

The figures below illustrate this graphically.



A B

[1] Zelinsky and Zelikow, *Ber.*, 1901, **34**, 2865.

[2] Vorländer and Mumme, *Ber.*, 1903, **36**, 1470 ; Vorländer and Hayakawa, *l.*, 3528 ; Vorländer, *Annalen*, 1903, **341**, 1 ; 1906, **345**, 155.

Let us take the case of the addition of an acid HX to the ketone R . CH : CH . CO . R as an example. In compounds of Class 𝔄 the acid HX has simply attached itself to the ketone to form a kind of double compound, which Vorländer represented thus—

$$\overset{(HX)}{R\,.\,CH\text{———}CH\,.\,CO\,.\,R}$$

Here no separation of HX into H and X occurs. But in the case of the stable bodies, Type 𝔅, this dissociation of the acid molecule does actually take place, so that we may write the formula of these bodies thus—

$$R\,.\,\overset{X}{C}H\text{———}\overset{H}{C}H\,.\,CO\,.\,R \quad \text{or} \quad R\,.\,\overset{H}{C}H\text{———}\overset{X}{C}H\,.\,CO\,.\,R$$

Now, in order that any addition-compound be formed there must exist between the two interacting molecules of acid and ketone a difference which Vorländer termed a difference in "potential." The amount of this difference can be estimated by measuring the velocity with which the two substances unite; for the greater the difference in potential between them, the more rapidly will they unite with each other. The formation of the coloured, unstable products is almost instantaneous, while the rate of formation of the stable type is quite measurable. From this we may conclude that the strain in the case of the formation of the unstable bodies is greater than that in the production of the isomers.

Vorländer expressed his view somewhat as follows. If we consider the case of two substances about to interact, the difference in potential between them may be called h. When the unstable compound is formed, only a very little energy is used up, and the difference in potential between the two components sinks to h_a, the rest of the original energy being utilized in holding the two components loosely together. Since there is little change of potential throughout the system, such reactions can take place rapidly even at low temperatures. In the case of the stable compounds, however, the difference in potential h is much reduced, say to h_b. On Vorländer's view, time is required to bring about this change in potential, and also to overcome certain reaction difficulties, so that the rate of addition is slow. Further, the two types of addition products, owing to the

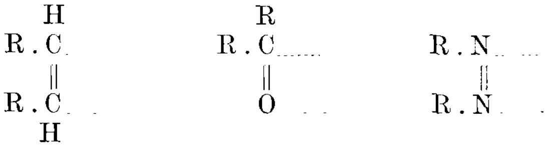
difference in potential between them, have quite different properties. Vorländer grouped the whole series of addition reactions according to their results, and in this way obtained the following series: (1) Compounds of Type 𝔄; (2) double salts; (3) complex salts; (4) compounds of Type 𝔅.

The difference between the two systems 𝔄 and 𝔅 is especially marked, when we take into consideration the nature of the solvent. In the case of 𝔄 the dielectric constant of the solvent will exercise a very marked influence; but in the case of 𝔅, since the compounds are in actual contact, the solvent will have no effect.

4. *Thiele's Theory of Partial Valencies*

In the foregoing theories the question of addition was treated from a broad standpoint, but now we must come to more restricted fields. It is very seldom that any theory is accepted immediately after being published; usually a considerable time is required during which the chemical world assimilates the author's views in a more or less unconscious manner, until some day they find their way into text-books. It is a remarkable tribute to the value of Thiele's theory, with which we are about to deal, that it became a classic almost as soon as it was published; and was not forced to undergo the process of cud-chewing which is usually the most that can be expected when a new theory is under consideration.

The Thiele theory [1] is based upon the following assumption. If we imagine the case of a double bond between two atoms, it is supposed that the whole of the affinity of the atoms is not used up, but that in addition to that which is utilized in joining the two atoms together there is a slight excess on each atom. This slight excess of valency Thiele designated by the name *Partial Valency*, and to its presence he attributed the additive power which unsaturated compounds display. To represent the partial valencies, Thiele employed a dotted line, thus—



[1] Thiele, *Annalen*, 1899, **306**, 87.

Take now a system of two double bonds arranged thus:

R—CH=CH—CH=CH—R

Since it contains a pair of double bonds, it might be expected to take up four atoms of hydrogen or bromine simultaneously, or at least to take up two atoms of bromine or hydrogen at one of the double bonds. In other words, we should expect to find one molecule of bromine attacking it first, with the formation of the compound—

R—CHBr—CHBr—CH=CH—R

to which another bromine molecule might be added, giving the tetrabromo-compound—

R . CHBr . CHBr . CHBr . CHBr . R

In practice, however, the first molecule of bromine does not attack either of the double bonds; it attacks them both at once, with the formation of the compound—

R . CHBr . CH : CH . CHBr . R

in which both of the original double bonds have disappeared, giving rise to a new double bond in the centre of the molecule. If we write out the scheme of partial valencies for the original substance—

R . CH : CH . CH : CH . R

it is evident that only the two at the ends of the system have the faculty of attracting bromine, the two middle partial valencies failing to act. In order to express this behaviour Thiele wrote the formula in the following way, in which the two central partial valencies are supposed to have neutralized one another:

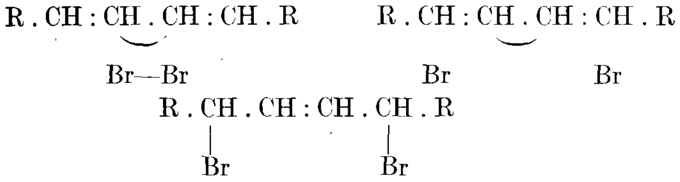
$$\mathrm{R{-}CH{=}\underbrace{CH{-}CH}{=}CH{-}R}$$

We can make this behaviour clear by supposing that the carbon atoms of the chain are charged alternately with positive and negative forces, the two central atoms will then neutralize one another, leaving the ends still charged—

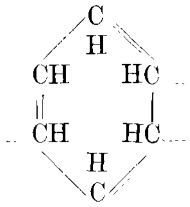
$$\mathrm{R\;.\;\overset{+}{CH}:\overset{-}{CH}\;.\;\overset{+}{CH}:\overset{-}{CH}\;.\;R} \qquad \mathrm{R\;.\;\overset{+}{CH}:\underbrace{CH\;.\;CH}:\overset{-}{CH}\;.\;R}$$

Such a system Thiele termed a *Conjugated Double Bond.*

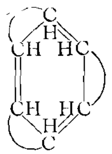
If addition takes place in the case of a conjugated double bond, obviously the two new atoms will attach themselves at the ends of the chain in the position indicated by the free partial valencies. But this does not end the matter, for no sooner has addition taken place than the conjugation is destroyed, and hence a new double bond will be formed between the central atoms of the system—



The most striking application of the Thiele theory, however, is found in the case of the benzene ring. If we write down the Kekulé formula for benzene, and fill in the partial valencies in the usual way, we arrive at the following figure :—



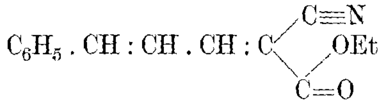
An examination of this system will show that it forms *a closed series of conjugated double bonds.* In other words, it can be written as shown below, and no free partial valencies exist in the system. Hence the impossibility of producing addition products with benzene under normal conditions is neatly symbolized on the Thiele theory ; and benzene can be formulated thus :

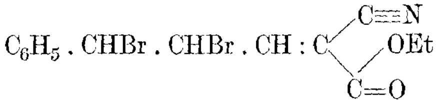


Though the partial valency theory has a widespread application, it is not infallible ; for several cases are known in which it

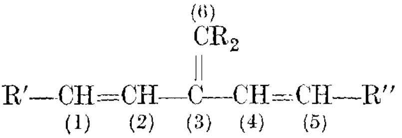
is not in accordance with the results of experiment. Too much stress should not be laid on these exceptions, but one or two of them may be mentioned here.

Harries [1] showed that unsaturated aldoximes or ketoximes may be reduced to unsaturated amines. Thiele himself mentioned a case observed by Bredt and Kallen [2] in which hydrocyanic acid adds on to cinnamylidene-malonic acid by simple addition to the double bond next the carboxyl radicle. Hinrichsen and Lohse observed that when cinnamenyl-cyanacrylic ester (I.) is allowed to react with bromine it yields a bromide of the formula (II.) shown below—

(I.) 

(II.) 

Inspection of the formula (I.) will reveal the fact that in it the conjugation is not a simple one wherein the conjugated linkages follow each other in a straight chain; for the right-hand ethylenic linkage is obviously conjugated with the double bond of the carbonyl group and also with the triple bond of the nitrile radicle. This is what is termed *crossed conjugation*,[3] of which the simplest type is found in compounds of the following structure:—

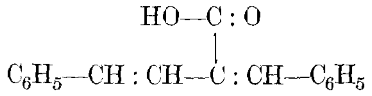


A glance at this system will show that it might be regarded as containing two different chains of conjugation. The atoms 1, 2, 3, and 6 are included in one chain; the atoms 6, 3, 4, and 5 are included in the second system. Now the manner in which such a system will react with an external reagent will naturally be governed to a large extent by the nature of the reagent and

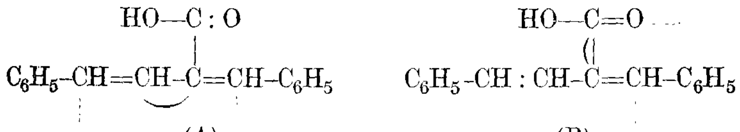
[1] Harries, *Annalen*, 1903, **330**, 185.
[2] Bredt and Kallen, *Annalen*, 1896, **293**, 338.
[3] Thiele, *Annalen*, 1899, **306**, 87.

the nature of the atoms carrying free partial valencies in the crossed conjugated system.

A concrete case will make this point clear, and for the sake of example, the reactions of dibenzalpropionic acid may be described. Its formula is—

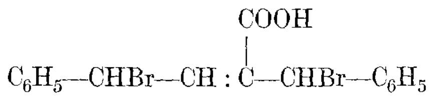


Now this structure can be regarded as containing both the chains of conjugation shown below:

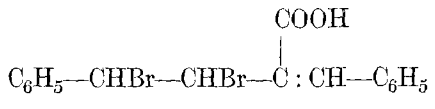


(A) (B)

Assume that bromine is brought into contact with dibenzalpropionic acid. How will it attack the various unsaturated linkages which present themselves? Bromine has more affinity for carbon than for oxygen. If a molecule of bromine attacks the system (A), it finds ready for it two partial valencies of two carbon atoms, to which it can readily fasten itself. On the other hand, if system (B) presents itself to the bromine molecule, one of the partial valencies is that of an oxygen atom, for which the bromine has no affinity. Obviously the bromine atoms will attack the system (A) by preference and produce the compound



In addition to this, there is the possibility of a formation to a slight extent of the compound

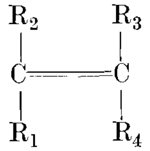


owing to the fact that partial valencies may exist on the carbon atoms concerned if the system is in the form (B) in which the main chain of conjugation is unfavourable to the reception of bromine.

5. *The Effect of Substituents on Double Bonds*

Though in the main the partial valency theory is most useful, in some cases it is necessary to take into account the influence exerted upon the addition reaction by substituents near the double bond.

This part of the subject has been investigated by Bauer,[1] who was able to substantiate Nef's view [2] that addition reactions may be influenced in this way. Bauer showed that if phenyl, carboxyl, or carbethoxyl groups or bromine atoms be accumulated in the neighbourhood of a double bond, bromine is not easily taken up by the double linking. For instance, if we take as an example the general formula—



and make R_1 a carboxyl group, bromine will be added on, unless the other R groups are bromine atoms, or bromine atoms with some methyl groups. Methyl groups alone do not hinder the addition. Thus we get addition of bromine in the cases of acrylic acid, α- and β-bromacrylic acids, crotonic and isocrotonic acids, dimethylacrylic acid, tiglic acid and trimethylacrylic acid. No addition of bromine takes place in the cases of tribromoacrylic and dibromo-crotonic acids.

If R_1 and R_4 be replaced by carboxyl groups, an addition of bromine remains possible, so long as R_2 and R_3 are not either bromine atoms or methyl radicles. Thus bromine will attack maleic, fumaric, mesaconic, or bromo-maleic acid ; but it will not attack the double bonds of dimethyl-fumaric, dibromofumaric, or bromo-mesaconic acid.

When R_1 is a phenyl radicle and the other three R's are methyl groups, the compound can take up a molecule of bromine. If R_1 and R_4 are phenyl groups, and one of the remaining R's is a hydrogen atom, the compound will react with bromine ; but if, in addition to the two phenyl groups, two bromine atoms be introduced, the additive power vanishes. Thus while addition

[1] Bauer, *Ber.*, 1904, **37**, 3488.
[2] Nef, *Annalen*, 1898, **298**, 208.

takes place with stilbene, methyl-stilbene, or bromo-stilbene, it fails in the case of dibromo-stilbene.

If phenyl groups be substituted for R_1 and R_2, while the two other R's are hydrogen atoms or alkyl groups, a new phase reveals itself; for here there is first an addition reaction and then a spontaneous loss of hydrobromic acid, leaving as the final product a bromo-substituted unsaturated compound. In this way behave diphenyl-ethylene, diphenyl-propylene, diphenyl-methyl-propylene; but no addition of bromine takes place in the cases of diphenyl-bromo-ethylene, diphenyl-bromo-propylene, or tetraphenyl-ethylene.

Bauer [1] also showed that, when placed near a double bond, the phenyl group had a certain effect upon the addition of bromine, the carbethoxyl group had more, while the nitrile group had the strongest influence of the three. It was also found that the influence of the phenyl group was weakened by nitration, a nitro-group in the meta-position having least effect, and one in the ortho-position the most influence. Bauer showed further that the addition of bromine to the double bond is a reversible reaction, equilibrium being attained at different stages according to the effect of the substituents introduced into the molecule.

It is a curious fact that substituents which influence the addition of bromine have a parallel effect upon the dissociation constant of acids, the effect of a phenyl group in the one case, for instance, being less than that of a cyanide radicle, and the same holding good in the case of the dissociation constants.

Somewhat similar results have been obtained by Klages [2] in the course of his researches on the reduction of styrolene derivatives.

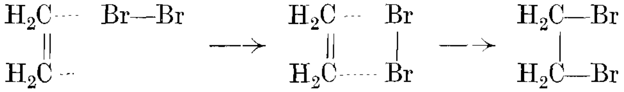
6. *Conclusion*

Before leaving the subject of addition reactions, we may return for a moment to the Thiele theory in order to deal with a point which was omitted during the general survey. Assuming the existence of partial valencies at each end of a double linkage, it is obvious that an addition reaction may be regarded as following either of two courses. In the first place, it may be taken

[1] Bauer, *J. pr. Chem.*, 1905, II, **72**, 201; Bauer and Moser, *Ber.*, 1907, **49**, 918.

[2] Klages, *Ber.*, 1903, **36**, 3584; 1904, **37**, 1721, 2301.

for granted—as has been done hitherto in this chapter—that the incoming reagent presents itself simultaneously to both partial valencies, as shown in (II.) below. Or, instead, it may be assumed that the initial stage of the reaction consists in the anchoring of the molecule of the incoming reagent[1] by one partial valency, as shown in (I.), with a subsequent action of the second partial valency to yield the system (II.).



(I.) (II.) (III.)

Results obtained with addition-products of chlorides such as $SnCl_4$ to ketones are said to support the idea that a molecular anchoring, as in (I.), actually occurs. Reddelien[2] has obtained compounds from ketones and nitric acid, such as $C_6H_5 . CO . CH_3,HNO_3$, which seem to be the initial products in the nitration of ketones. The evidence in the whole matter is not conclusive.

The foregoing brief account of the various theories of addition reactions only serves to throw into relief the insufficiency of our present views on this subject. On the one hand, we have ideas which are so vague as to convey very little meaning, while on the other we have mechanical hypotheses which are too inelastic to cover anything but a very narrow field. The most useful of all the suggestions hitherto put forward, Thiele's partial valencies, deals rather with the facts themselves than with any explanation of them, and takes little account of subtle differences in reactivity. The field is tempting to the theorist, however, and perhaps before long we may have some view which will combine the advantages of all the present hypotheses without their drawbacks.

[1] Tschitschibabin, *J. pr. Chem.*, 1912, **86**, 381; Pfeiffer, *Annalen*, 1910, **376**, 285; 1911, **383**, 92; 1914, **404**, 13; Stewart, *Stereochemistry* (1919), p. 118; Wohl, *Ber.*, 1919, **52**, 52.

[2] Reddelien, *J. pr. Chem.*, 1915, **91**, 213.

CHAPTER IV

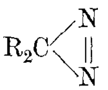
THE ALIPHATIC DIAZENE COMPOUNDS

1. *The Constitution of the Diazene Diazo-derivatives*

THE structures of the aromatic diazo-compounds gave rise to a prolonged and vivacious controversy; * and the solution was reached only after almost every possible formula had been discussed and brought to the test of experiment. The history of the aliphatic diazo-compounds has been different. In their case, a certain structure was assumed on their discovery, remained unopposed for years, and was finally supplanted, almost without contention, by a newer mode of formulation.

The aliphatic diazo-compounds do not form exact parallels to the aromatic derivatives. No diazonium salts are known which would correspond to the aromatic diazonium salts; and the list of aliphatic diazotates, diazo-cyanides, and diazo-sulphonates is a very restricted one. By far the greatest number of diazo-derivatives in the aliphatic series belong to the so-called *diazene* group of which diazomethane, $CH_2 : N_2$, is the parent substance; and it is upon this group that attention will be concentrated in the present chapter.

Two formulæ have been suggested for the diazene derivatives:

(I.) 

(II.) $R_2C : N \equiv N$

The first of these was proposed by Curtius and Lang [1] on the discovery of the aliphatic diazo-compounds; the second was

* For an interesting account of the polemics in this case, Lachman's *Spirit of Organic Chemistry* should be consulted.

[1] Curtius and Lang, *J. pr. Chem.*, 1891, (2), **44**, 554.

originally put forward by Angeli,[1] and was again suggested, later, by Thiele.[2] Since the structures of much more complex materials are well-established, it may seem strange that the constitution of diazomethane, which contains only five atoms, has not been placed absolutely beyond doubt; but it cannot be denied that there is still a loophole for contention in this matter, and even in the simpler case of azoimide, N_3H, the formula cannot be regarded as settled beyond controversy. The preponderance of evidence is in favour of the open-chain formulæ, however, as will be seen in due course.

Before entering upon the pros and cons of the question, as between the two structures shown above, it seems advisable to consider the matter from a different standpoint. Since the formula of diazomethane can be written in either of two ways, it may be suggested that the compound as we know it may actually be an equilibrium mixture of the two isomeric varieties; so that the case would be analogous to that of the pseudo-acids.

Now in practice, only one form of diazomethane is known; no second isomer has ever been detected. An inspection of the formulæ below will reveal a fundamental difference between the two types:

Nitromethane	$\begin{array}{c} R_2C{=}N{=}O \\ \quad\;\; \vert \\ \quad\;\; OH \end{array}$	$R_2CH{-}N\begin{array}{l} \nearrow O \\ \searrow O \end{array}$
Diazomethane	$R_2C{=}N{\equiv}N$	$R_2C\begin{array}{l} \diagup N \\ \quad\; \Vert \\ \diagdown N \end{array}$

In the case of nitromethane, the change from the *aci*-form to the normal form necessitates the wandering of a hydrogen atom from oxygen to carbon; but in the diazene formulæ, a mere rearrangement of affinity within the molecule is all that is required in order to convert one structure into the other. Since the transfer of the material hydrogen atom in the pseudo-acids is a process which in many cases takes place with a measurable velocity, it is possible to isolate the normal from the isomeric *aci*-form. But a mere rearrangement of affinity within the

[1] Angeli, *Gazzetta*, 1894, **24**, II. 46; *Atti R. Accad. Lincei*, 1907, **16**, II, 790; 1911, **20**, I, 626.

[2] Thiele, *Ber.*, 1911, **44**, 2197.

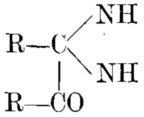
molecule might be expected to be practically instantaneous ; and thus, even if diazomethane exists in two isomeric forms, the isolation of one variety in a pure state may be experimentally impossible. The case of the diazene compounds, in fact, is much more akin to the benzene oscillation phases of Kekulé than to the pseudo-acid type ; and there is really no more reason for believing that diazomethane can be isolated in two forms than there is for supposing it possible to separate two of the benzene "oscillation phases" from each other.

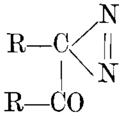
Thus when discussing the problem of cyclic versus open-chain structures for the diazene derivatives, it must be borne in mind that these substances may quite well be supposed to pass from one mode of linking to the other with the least possible change in internal energy ; and all that can really be settled in the matter is best method of formulating a reaction which is observed in practice.

When hydrazine acts on simple ketones or aldehydes, the products are hydrazones having the structure $R_2C:N.NH_2$; and these bodies, in presence of excess of ketone or aldehyde, yield ketazines, $R_2C:N.N:CR_2$. On trying analogous reactions with benzil or the α-ketonic esters, Curtius [1] found that in these cases the products showed no avidity for condensation with extra molecules of aldehyde or ketone. On oxidation, also, the two classes showed differences in behaviour. The derivatives of the simple ketones yielded unstable tetrazone derivatives of the type $R_2C:N.N:N.N:CR_2$; whereas the products from the dicarbonyl compounds were oxidized to aliphatic diazo-derivatives.

In order to express this difference between the two series, the hydrazine derivatives of the simple ketones were written in the form (I.), whilst the corresponding substances derived from dicarbonyl compounds were given the cyclic formula (II.) and

(I.) $R_2C:N.NH_2$

(II.) 

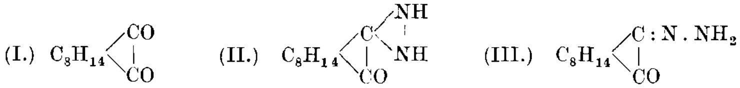
(III.) 

in this way the cyclic representation made its appearance, since obviously the oxidation product of (II.) must have the structure

[1] Curtius and others, *J. pr. Chem.*, 1889, (2), **44**, 161, 544 ; 1911, (2), **83**, 217.

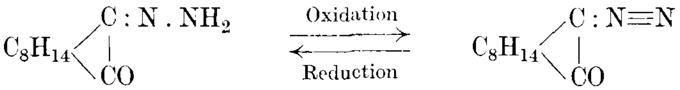
(III.), which would therefore represent the diazene-type on this hypothesis.

This reasoning was completely destroyed by the work of Forster and Zimmerli[1] on the hydrazones of camphorquinone (I.). Two isomeric hydrazones were shown to exist; and obviously only one of these could be represented by the hydrazi-form (II.); so the other isomer must have the structure (III.).

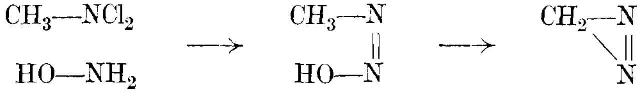


Now in practice, both hydrazones are oxidized to diazocamphor; and from this diazocamphor, by reduction, a mixture of the two hydrazones can be obtained. The only explanation of this is to assume that the two hydrazones are stereoisomers with the structure (III.) and that neither of them has the structure (II.). But since camphorquinone is an α-dicarbonyl compound, this proves that the hydrazones of such substances have exactly the same constitution as those derived from simple ketones. Thus the necessity of the cyclic formulation disappears, so far as its original utility is concerned.

The open-chain formula, on the other hand, expresses these reactions in the simplest manner, as shown below:



Another argument which might be adduced in favour of the cyclic formula is that based on the production of diazomethane by the action of hydroxylamine upon methyl-dichloramine:



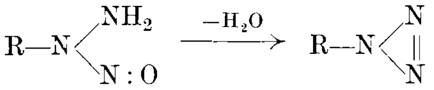
Formulated in this manner, the reaction appears to lend support to the cyclic representation; but it must be remembered that the compound CH_3—N : N—OH might quite conceivably yield the open chain CH_2 : N$\equiv$N by the loss of a molecule of water from the same two atoms as in the cyclic case. Obviously this reaction is equally useful on either side of the controversy.

An examination of the absorption spectra of the aliphatic

1 Forster and Zimmerli, *J.*, 1910, **97**, 2156.

diazo-compounds led Hantzsch and Lifschitz [1] to the conclusion that the ring-structure was the best representation of these substances; but nowadays evidence drawn from absorption spectra is hardly allowed the weight which was lent to it at one time.

Curiously enough, the best argument in favour of the cyclic structure is furnished, not by the diazene compounds themselves, but by the azoimides. These compounds can be obtained from nitrosohydrazines by elimination of water:



This reaction seems to prove the existence of the azo-group —N : N— as part of a three-membered ring; and if it can exist in the azoimides, it might equally be found in the diazene series which resemble the azoimides in several respects.

One of the strongest arguments against the cyclic structure, however, has yet to be mentioned. The aliphatic diazo-compounds readily unite with many substances to form heterocyclic derivatives wherein two nitrogen atoms play the part of adjacent members of the rings. Now an inspection of the formulæ below will show that in the open-chain structure, such a reaction could take place by simple attachment of two ends of a carbon chain to the atoms marked with asterisks. In the case of the cyclic formula, on the other hand, the ring must first be ruptured; and if the two nitrogen atoms are to be left united to each other, this break-up must occur at the dotted line. In other words, though on all normal ideas the double bond of the —N : N— group would furnish the point of attack of a fresh reagent, it is kept intact and a single linkage between two atoms is broken instead. A

concrete example will make the matter clear. Diazomethane attacks acetylene and produces pyrazole. As can be seen from the formulæ below, this reaction can be clearly expressed by using the open-chain structure for diazomethane. The double and triple bonds of the diazomethane molecule open up and unite

[1] Hantzsch and Lifschitz, *Ber.*, 1912, **45**, 3022.

with the bonds set free by a corresponding opening-up of the acetylene system :

In the case of the cyclic diazomethane formula, the double bond of the —N : N— group might be expected to react with the triple bond of the acetylene molecule, and the result would be a synthesis of glyoxaline instead of pyrazole :

The only alternative assumption is that the three-membered ring splits open between the carbon and nitrogen before attacking the acetylene ; but such a rupture, even if probable, would simply lead to the formation of the normal open-chain structure of diazomethane. Thus in order to account for the reaction, the open-chain structure must be assumed at one point in the process ; and since there is so little evidence in favour of the cyclic grouping, it seems simplest to leave it aside and start with the open-chain structure for the diazene derivative.

It is unnecessary here to accumulate further evidence in favour of the open-chain structure. In the rest of this chapter it will be used in the equations ; and the reader will be able to see that it is in agreement with all the normal reactions of the aliphatic diazo-compounds.

2. *The Preparation of Aliphatic Diazene Compounds*

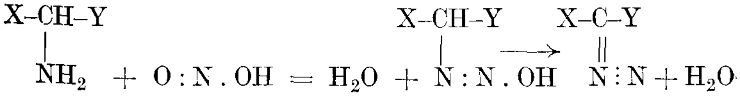
1. The action of nitrous acid upon primary amines is largely controlled by the character of the nucleus to which the $—NH_2$ radicle is attached. In the aromatic series, for example, an amino-group in a side-chain yields the corresponding alcoholic radicle when treated with nitrous acid, no isolable diazo-compound being obtained during the reaction ; but if the amino-group be directly joined to the benzene nucleus, the reaction may proceed in two stages : the formation of a semi-stable diazo-derivative, and its subsequent decomposition. It should be noted that in this second case the amino-group is in the α-position to the unsaturated group —CH : C— of the benzene ring.

A similar state of things is found in the case of the aliphatic amines. In order that a diazene derivative may be formed, two conditions must be fulfilled. First, there must be one hydrogen atom attached to the same carbon atom as the amino-group. Second, there must be an unsaturated group such as carbonyl or cyanide radicle directly attached to the carbon atom carrying the amino-group. If these conditions are not fulfilled, then the action of nitrous acid upon the amine yields only an alcohol and not an isolable diazene derivative. For example, when nitrous acid acts upon $\alpha\beta$-diamino-propionic ester (I.), the result [1] is β-hydroxy-α-diazo-propionic ester (II.):

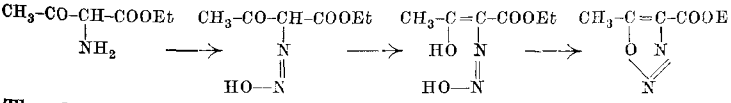
$$NH_2 \,.\, CH_2 \,.\, CH(NH_2) \,.\, COOEt \quad \text{(I.)} \qquad HO \,.\, CH_2 \,.\, C(N_2) \,.\, COOEt \quad \text{(II.)}$$

Inspection will show that the amino-group in the α-position to the unsaturated —COOEt radicle has been transformed into a diazene group; whereas the other amino-radicle, with no unsaturated group in the α-position, has yielded a hydroxyl group.

This method of preparing diazo-derivatives can be symbolized as follows:



In these formulæ, either X or Y is assumed to be an unsaturated group like —CO—, —C≡N, or —COOEt. In the case of the α-amino-β-ketonic esters, R . CO . $CH(NH_2)$. COOR, both groups X and Y belong to this category, and the reaction [2] has been assumed to take the course shown below:



The final product is termed a diazo-anhydride. An objection has been raised against this formulation of the diazo-anhydrides, on the ground that these anhydrides should exist in two isomeric forms:

[1] Curtius and Müller, *Ber.*, 1904, **37**, 1278.

[2] Wolff, *Annalen*, 1902, **325**, 129; 1904, **333**, 1; 1912, **394**, 23; *Ber.*, 1903, **36**, 3612.

Since no such isomerism has been observed, it is suggested that the "diazo-anhydrides" are simply β-dicarbonyl derivatives of the type R . CO . $C(N)_2COOR$.

It is obvious that this method cannot be used for preparing the diazo-paraffins such as diazomethane; for in their case the original amino-compounds, such as methylamine, do not contain the unsaturated radicle which is necessary for the production of a diazo-derivative.

2. Another method of obtaining diazo-derivatives of the fatty acids has been discovered in the reduction of isonitraminic compounds. When acetoacetic ester or its mono-alkyl derivatives are treated with nitric oxide, they yield sodium salts of α-isonitraminic-acetoacetic acids. On warming these salts with excess of alkali, salts of isonitraminic-fatty acids [1] are produced:

$$\underset{\text{HO-N-NO}}{CH_3\text{-CO-}\overset{}{CR}\text{-COONa}} + 2NaOH = CH_3\text{-COONa} + H_2O + \underset{\text{HO-N-NO}}{CHR\text{-COONa}}$$

When these last salts are reduced by means of sodium amalgam, diazo-derivatives are produced:

$$HO\text{—}N(NO)\text{—}CHR\text{—}COONa + H_2 = N : N : CR\text{—}COONa + 2H_2O$$

A parallel reaction [2] leads to the formation of diazo-paraffins. On treatment with anhydrous nitric acid, monoalkyl-urethanes yield nitro-derivatives which break up under the action of ammonia. Ammonium salts of aliphatic nitramines are thus produced, from which the nitramines themselves can be obtained by boiling with alcohol:

$$\underset{\text{Methyl-urethane}}{CH_3\text{—}NH\text{—}COOEt} \rightarrow \underset{\text{Nitro-derivative}}{CH_3\text{—}N(NO_2)\text{—}COOEt} \rightarrow \underset{\text{Methyl-nitramine}}{CH_3\text{—}NH.NO_2}$$

The alkyl-nitramines form salts of the type: CH_3—N : NO—ONa, which by careful reduction can be converted into diazo-paraffins:

$$CH_3\text{—}N : NO\text{—}ONa \longrightarrow CH_2 : N : N$$

3. Both the diazo-paraffins and their substitution-products can be obtained by the oxidation of hydrazones with mercuric oxide. This reaction was discovered by Curtius,[3] but its true character was first recognized by Forster and Zimmerli.[4] Two examples of it may be given here:

[1] Traube, *Ber.*, 1896, **29**, 667.
[2] Thiele and Meyer, *Ber.*, 1896, **29**, 961.
[3] Curtius and Thun, *J. pr. Chem.*, 1891, (2), **44**, 161.
[4] Forster and Zimmerli, *J.*, 1910, **97**, 2156.

$$NH_2 . N : C \langle {CH_3 \atop COOEt} + HgO = N : N : C \langle {CH_3 \atop COOEt} + Hg + H_2O$$

$$NH_2 . N : C(C_6H_5)_2 + HgO = N : N : C(C_6H_5)_2 + Hg + H_2O$$

4. The next two methods are applicable only to the formation of diazo-paraffins. When alkyl-urethanes are treated with nitrous acid, they yield nitroso-alkyl-urethanes which, under the action of alkali, give diazo-derivatives :

$$\begin{array}{l} CH_3—NH \\ \quad | \\ \quad COOEt \end{array} \longrightarrow \begin{array}{l} CH_3—N—NO \\ \quad | \\ \quad COOEt \end{array} \longrightarrow \begin{array}{r} CH_3—N \\ \| \\ KO—N \end{array} \longrightarrow \begin{array}{c} CH_2 \\ \| \\ N : N \end{array}$$

It may be noted that a diazotate [1] is one of the intermediate products in this series of reactions.

5. A process analogous to the foregoing is used in order to obtain diazo-paraffins from monoalkyl-hydrazines. These compounds of the type R . NH . NH_2 are treated with nitrous acid ; and thus nitroso-alkylhydrazines, R . N(NO) . NH_2 are formed. Under the joint action of alkyl nitrite and alkali,[2] nitrous oxide and alcohol are split off and diazotates are produced ; and these yield the required diazo-paraffins just as in the foregoing methods. The final stage in the decomposition of methyl-nitroso-hydrazine will illustrate the process—

$$CH_3—N(NO)—NH_2 + KOH + EtO . N : O$$
$$= CH_3—N : N—OK + N_2O + EtOH + H_2O$$

6. By the action of bleaching-powder on methyl-ammonium chloride, methyl-dichloramine is formed ; and this, on treatment with hydroxylamine,[3] yields diazomethane :

$$CH_3\text{-}NCl_2 + H_2N . OH \xrightarrow{-H_2O} CH_3\text{-}N : N\text{-}OH \xrightarrow{-H_2O} CH_2 : N{\equiv}N$$

7. A method of preparation [4] having some value from the practical standpoint consists in treating hydrazine with chloroform and alkali :

$$NH_2 . NH_2 + CHCl_3 + 3KOH = N{\equiv}N : CH_2 + 3KCl + 3H_2O$$

It is hardly necessary to point out the obvious parallelism between

[1] Hantzsch and Lehmann, *Ber.*, 1902, **35**, 900.
[2] Thiele, *Annalen*, 1910, **376**, 252.
[3] Bamberger and Renauld, *Ber.*, 1895, **28**, 1682.
[4] Staudinger and Kupfer, *Ber.*, 1912, **45**, 501.

this process and the usual carbylamine reaction used as a test for primary amines.

8. One of the most useful methods of preparing diazomethane for methylation purposes is to decompose nitroso-methyl-urea with potassium hydroxide : [1]

$$CH_3 . N(NO) . CO . NH_2 + KOH = CH_2 : N \equiv N + KOCN + 2H_2O$$

Since nitroso-methyl-urea is easily prepared by the action of nitrous acid on methyl-urea, this reaction forms a simple way of preparing diazomethane. Werner has shown that it proceeds without loss when alcohol is present, so that by means of it an alcoholic solution of diazomethane can be obtained ; and by this method alcohol-soluble substances can readily be methylated.

3. *Some Reactions of the Aliphatic Diazene Compounds*

In the space available here, it would be quite impossible to deal with all the modes of reaction of which the aliphatic diazo-compounds are capable ; and therefore in the following survey the main object will be to give a general idea of the principal results obtained in the field. Speaking in very general terms, the reactions of the fatty diazene derivatives can be grouped into three sets : (1) Reactions resulting in the elimination of a molecule of nitrogen ; (2) Reactions leaving the nitrogen chain intact as part of an open chain ; and (3) Reactions which lead to the formation of heterocyclic rings containing the two nitrogen atoms of the diazo-compound. These groups will now be taken up in turn ; and, for convenience of reference, the reagents employed along with the diazo-derivative will be noted at the beginning of the paragraphs.

Halogens.[2]—A molecule of a halogen replaces the diazene group :

$$Br_2 + N : N : CH_2 = Br_2CH_2 + N_2$$
$$Br_2 + N : N : CH . COOEt = Br_2CH . COOEt + N_2$$

Water.[3]—The diazene group is replaced by a molecule of water, with the formation of a primary alcoholic radicle :

$$H_2O + N : N : CH_2 = CH_3OH + N_2$$
$$H_2O + N : N : CH . COOEt = HO . CH_2 . COOEt + N_2$$

[1] E. A. Werner, *J.*, 1919, **115**, 1093. [2] Pechmann, *Ber.*, 1894, **27**, 1889.
[3] Pechmann, *Ber.*, 1894, **27**, 1888.

Alcohols.[1]—Elimination of the diazene group leads to ether formation:

$$C_2H_5OH + N \vdots N : CH_2 = C_2H_5 . O . CH_3 + N_2$$
$$C_2H_5OH + N \vdots N : CH . COOEt = C_2H_5 . O . CH_2 . COOEt + N_2$$

The replacement of the diazo-group by a hydrogen atom, which takes place in the aromatic diazo-compounds, is not paralleled by the diazene group of the fatty series.

Aldehydes.[2]—Ketones or ketonic esters are formed:

$$C_6H_5 . CO . H + N \vdots N : CH_2 = C_6H_5 . CO . CH_3 + N_2$$
$$C_6H_5.CO.H + N \vdots N : CH.COOEt = C_6H_5.CO.CH_2.COOEt + N_2$$

Acids.[3]—When treated with carboxylic acids, the diazo-derivatives yield the corresponding esters:

$$CH_3 . COOH + N \vdots N : CH_2 = CH_3 . CO . O . CH_3 + N_2$$
$$C_6H_5.COOH + N \vdots N:CH.COOEt = C_6H_5.CO.O.CH_2.COOEt + N_2$$

When halogen acids[4] are employed, the reaction is almost explosive in violence, and the diazene group is replaced by one molecule of hydrogen halide:

$$HCl + N \vdots N : CH_2 = CH_3 . Cl + N_2$$
$$HCl + N \vdots N : CH . COOEt = Cl . CH_2 . COOEt + N_2$$

Hydrofluoric acid[5] is exceptional, however, for with diazoacetic ester it yields the ester of diglycollic acid by the addition of one molecule of water to, and removal of the nitrogen from, two molecules of the ester:

$$H_2O + \begin{array}{l} N \vdots N : CH . COOEt \\ N \vdots N : CH . COOEt \end{array} = O\!\begin{array}{l} \diagup CH_2 . COOEt \\ \diagdown CH_2 . COOEt \end{array} + 2N_2$$

Hydrocyanic Acid.[6]—With diazomethane, hydrocyanic acid ves rise to acetonitrile and carbylamine:

$$HCN + N \vdots N : CH_2 \begin{array}{l} \nearrow CH_3 . C \equiv N + N_2 \\ \searrow CH_3 . N \equiv C + N_2 \end{array}$$

[1] Curtius, *J. pr. Chem.*, 1888, (2), **38**, 423.
[2] Curtius and Buchner, *Ber.*, 1885, **18**, 2371; Schlotterbeck, *Ber.*, **1907**, 3000; 1909, **42**, 2565.
[3] Pechmann, *Ber.*, 1895, **28**, 858.
[4] Curtius, *J. pr. Chem.*, 1888, (2), **38**, 429.
[5] Holmberg, *Ber.*, 1914, **47**, 165.
[6] Pechmann, *Ber.*, 1895, **28**, 857; Peratoner and Palazzo, *Gazzetta*, 1908, I., 102.

Acyl Halides.—The action of substances like benzoyl chloride depends upon the constitution of the diazene derivative which takes part in the reaction. With the diazo-paraffins, halogen-substituted ketones [1] are produced :

$$C_6H_5.CO.Cl + N\vdots N:CH_2 = C_6H_5.CO.CH_2Cl + N_2$$

Diazoacetic ester, on the other hand, undergoes an entirely different change [2] when acted on by benzoyl chloride. Two molecules of diazoacetic ester interact with one molecule of the acid chloride, yielding chloracetic ester and benzoyl-diazoacetic ester :

$$\begin{array}{l} C_6H_5\text{-}CO \\ \quad | \\ \quad Cl \end{array} + \begin{array}{l} N\vdots N:CH.COOEt \\ N\vdots N:CH.COOEt \end{array} = \begin{array}{l} C_6H_5\text{-}CO\text{-}C(N_2)\text{-}COOEt \\ Cl\text{—}CH_2\text{—}COOEt \end{array} + N_2$$

This reaction obviously provides a method of introducing acid radicles into diazoacetic ester and analogous compounds.

Amines.—Here the reaction follows a normal course ; nitrogen is split off and its place is taken by a molecule of the amine :

$$C_6H_5.NH_2 + N\vdots N:CH_2 = C_6H_5.NH.CH_3 + N_2$$

$$C_6H_5.NH_2 + N\vdots N:CH.COOEt = C_6H_5.NH.CH_2.COOEt + N_2$$

Nitrogen Peroxide.[3]—Diazoacetic ester takes up two molecules of nitrogen peroxide, attaching them at the points left vacant by the elimination of the diazene group :

$$2NO_2 + N\vdots N:CH.COOEt = (NO_2)_2CH.COOEt + N_2$$

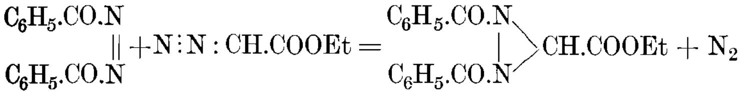
Nitroso-compounds.[4] — When true nitroso - compounds act upon aliphatic diazo-derivatives, the diazene group is replaced by the nitroso-compound with the formation of a nitrone :

$$C_6H_5\text{—}N:O + N\vdots N:C(C_6H_5)_2 = (C_6H_5)_2C{=}\underset{\displaystyle C_6H_5}{\overset{}{N}}{=}O + N_2$$

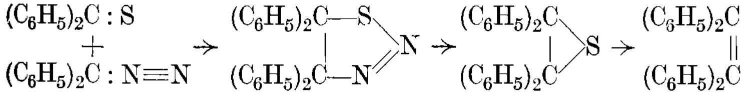
This reaction takes place with either diazo-hydrocarbons or carbonyl-diazocompounds ; but it cannot be carried out with nitrosamines or alkyl nitrites, despite the fact that both of the latter have nitroso-groups in their structures.

[1] Clibbens and Nierenstein, *J.*, 1915, **107**, 1491.
[2] Staudinger and others, *Ber.*, 1916, **49**, 1978.
[3] Wieland and Reisenegger, *Annalen*, 1913, **401**, 244.
[4] Staudinger and Miescher, *Helv. Chim. Acta*, 1919, **2**, 554.

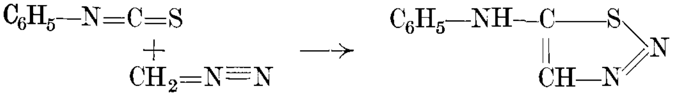
Azo-compounds.[1]—It has been found that azodibenzoyl is attacked by diazoacetic ester with the formation of the dibenzoyl-hydraziacetic ester shown below:



Thioketones.—Aldehydes, it may be recalled, yield acyl derivatives when acted on by diazene compounds; but ketones fail to react at all. The thioketones[2] show more reactivity; but in their case the reaction takes a different course, yielding derivatives of ethylene sulphide, from which hydrocarbons can be obtained by further heating. Except in one case, the initial products are labile and pass directly into sulphides:

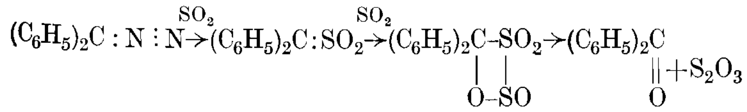


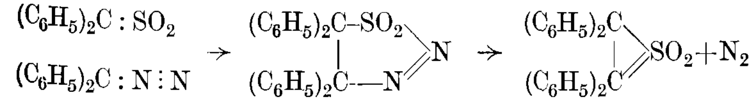
The proof of the correctness of this interpretation of the reaction is found in the case of phenyl thiocyanate and diazomethane:



Here the thiodiazole is a stable compound, and its structure can be established definitely.

Sulphur Dioxide.—According to the reaction-conditions, either benzophenone or tetraphenylethylene sulphone is produced by the action of diphenyldiazomethane upon sulphur dioxide.[3] The reactions leading to these products may be symbolized thus:





[1] Staudinger and Gaule, *Ber.*, 1916, **49**, 1961.
[2] Staudinger and Siegwart, *Helv. Chim. Acta*, 1920, **3**, 833.
[3] Staudinger and Pfenninger, *Ber.*, 1916, **49**, 1941.

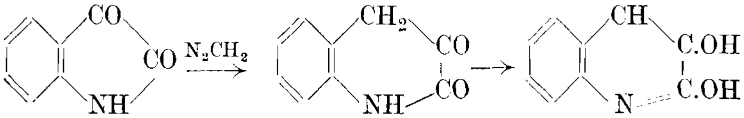
Aromatic Hydrocarbons.—When benzene derivatives [1] are treated with diazoacetic ester, they yield compounds containing dicyclic systems derived from nor-carane :

$$\begin{array}{l} CH{=}CH{-}CH \\ | \qquad\qquad \| \\ CH{=}CH{-}CH \end{array} + N:N:CH.COOEt = \begin{array}{l} CH{=}CH{-}CH \\ | \qquad\qquad | \\ CH{=}CH{-}CH \end{array}\!\!\!>CH.COOEt + N_2$$

The compound shown in the above formula undergoes a peculiar rearrangement when the temperature is raised. Part of it is converted into phenyl-acetic ester by rupture of the three-membered ring, whilst the remainder, by a disruption of the six-membered system, yields a heptamethylene derivative of the following structure :

$$\begin{array}{l} CH{=}CH{-}CH \\ | \\ CH{=}CH{-}CH_2 \end{array}\!\!>C{-}COOEt$$

Isatin.—In the case of isatin, the reaction again takes an unexpected turn ; for the five-membered ring is expanded to a six-membered one by the introduction of a methylene group—



Two cases may be mentioned here in which the diazene derivatives undergo decomposition in the absence of a second reagent. Under certain conditions, some aliphatic diazo-compounds yield ethylene derivatives and nitrogen, as shown below for the case of diazoacetic ester : [2]

$$\begin{array}{l} N:N:CH.COOEt \\ N:N:CH.COOEt \end{array} = 2N_2 + \begin{array}{l} CH.COOEt \\ \| \\ CH.COOEt \end{array}$$

It is assumed that the elimination of the nitrogen leaves free two divalent radicles, which then unite to form the ethylenic compound. When two diazene groups are in the α-position to each other in the molecule, this reaction produces an acetylene derivative. For example, diphenyl-bisdiazoethane, $C_6H_5{-}C(N_2){-}C(N_2){-}C_6H_5$, yields tolane, $C_6H_5{-}C{\equiv}C{-}C_6H_5$.

Again, when certain keto-diazo-derivatives are heated, they

[1] Buchner, *Ber.*, 1900, **33**, 684, 3453 ; 1901, **34**, 982 ; 1903, **36**, 3502 ; 1904, **37**, 931.

[2] Darapsky, *Ber.*, 1910, **43**, 112.

lose nitrogen and yield ketens.[1] For example, diphenyl-keten can be obtained from benzoyl-phenyldiazomethane:

$$\begin{array}{c}C_6H_5—CO—C:N:N\\ |\\ C_6H_5\end{array} = \begin{array}{c}C_6H_5—C:C:O\\ |\\ C_6H_5\end{array} + N_2$$

In some cases, the intramolecular change does not stop at this point and further alterations are observed; but these can be reduced to a minimum by keeping the temperature low and facilitating the evolution of the nitrogen by employing a solvent such as xylene and putting in some fragments of platinum to make bubble-formation easy.[2]

Turning now to cases in which the nitrogen of the diazene compounds is retained in the molecule as part of an open chain, we reach a group of reactions much more restricted than the one which has just been described.

Of considerable theoretical importance is the reduction of the diazene compounds by means of hydrogen and colloidal platinum. Here there is no reagent present which could induce intramolecular change in the reaction-product. Reduced in this manner, the diazene compounds yield hydrazones, along with a certain amount of hydrocarbon.[3] Possibly the formation of the latter product is due to the production of a di-imido-derivative which then loses nitrogen, as symbolized below:

$$(C_6H_5)_2C:N:N \begin{array}{l}\nearrow (C_6H_5)_2CH—N:NH \rightarrow (C_6H_5)_2CH_2 + N_2\\ \searrow (C_6H_5)_2C:N.NH_2\end{array}$$

Hydrogen sulphide when acting as a purely reducing agent[4] also yields hydrazones. The importance of the hydrazone formation in this reaction will appear later when the constitution of the diazene derivatives comes under consideration.

Reduction of diazoacetic ester by means of ferrous sulphate and a minimum of alkali[5] yields salts of hydrazi-compounds which on treatment with acids decompose into hydrazine salts and glyoxylic acid:

[1] Schröter, *Ber.*, 1909, **42**, 2346.
[2] Staudinger and Hirzel, *Ber.*, 1916, **49**, 2522.
[3] Staudinger and others, *Helv. Chim. Acta*, 1921, **4**, 21.
[4] Dimroth, *Annalen*, 1910, **373**, 338; Wolff, *ibid.*, 1912, **394**, 24.
[5] Curtius and Jay, *Ber.*, 1899, **27**, 777.

$$N\vdots N{:}CH.COOEt \rightarrow \begin{matrix} NH \\ | \\ NH \end{matrix}\!\!>\!CH.COOEt \rightarrow N_2H_4.H_2SO_4 + CHO.COOH$$

Many diazene compounds break down spontaneously into ketazine derivatives. Since nitrogen is liberated during the change, it has been assumed [1] that one molecule of the diazene derivative splits off nitrogen; and the divalent radicle so produced at once unites with a second molecule of the diazene derivative :

$$(C_6H_5)_2C:N\vdots N \xrightarrow{-N_2} (C_6H_5)C: + N_2C(C_6H_5)_2 = (C_6H_5)_2C:N{-}N:C(C_6H_5)_2$$

The action of the Grignard reagent also leads to the production of open-chain nitrogen derivatives, since diazomethane and phenyl magnesium bromide yield benzaldehyde phenylhydrazone.[2] In this case the reactions are rather complex. In the first place, one molecule of phenyl magnesium bromide attaches itself to the diazene group :

$$\begin{matrix} C_6H_5 \\ Br \end{matrix}\!\!>\!Mg + N\vdots N:CH_2 = \begin{matrix} C_6H_5 \\ Br.Mg \end{matrix}\!\!>\!N{-}N{=}CH_2$$

A rearrangement apparently follows, leading to diazobenzyl, which is then attacked by a second molecule of the Grignard reagent, yielding the compound shown below—

$$\begin{matrix} C_6H_5{-}CH_2 \\ Br.Mg \end{matrix}\!\!>\!N:N \xrightarrow{C_6H_5.Mg.Br} \begin{matrix} C_6H_5{-}CH_2 \\ Br.Mg \end{matrix}\!\!>\!N{-}N\!<\!\begin{matrix} C_6H_5 \\ Mg.Br \end{matrix}$$

On breaking up this intermediate product, phenyl-benzylhydrazine, $C_6H_5 . CH_2 . NH . NH . C_6H_5$, is liberated, which is spontaneously oxidized to benzaldehyde phenylhydrazone: $C_6H_5 . CH : N . NH . C_6H_5$.

An unexpected reaction is observed between diazene derivatives and tertiary phosphines, whereby phosphazines are formed.[3]

$$R_2C:N\vdots N + PR_3 = R_2C:N{-}N:PR_3$$

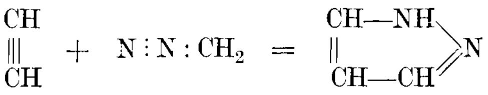
The phosphazines are extremely reactive substances; but curiously enough, in certain cases it is possible to regenerate

[1] Staudinger, *Ber.*, 1916, **49**, 1886.
[2] Zerner, *Monatsh.*, 1913, **34**, 1469, 1609.
[3] Staudinger and others, *Helv. Chim. Acta*, 1920, **2**, 619 ; 1922, **5**, 75.

the original diazene compound by heating the phosphazine in vacuo.

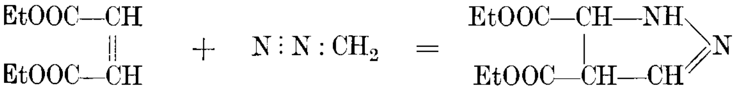
We must now turn to a series of reactions leading to cyclic compounds which contain the nitrogen atoms of the diazene group as ring-members.

Acetylene [1] and its derivatives react with diazomethane to yield pyrazole and its allies :

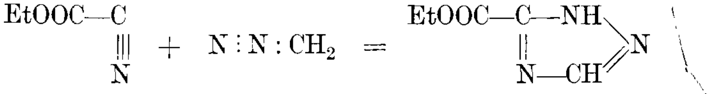


Quinones [2] also, in some peculiar way, give rise to pyrazole compounds by the action of diazomethane.

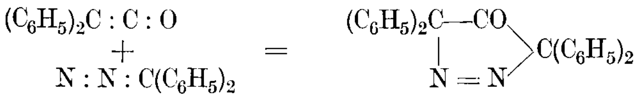
The ethylenic bond can also be attacked by diazomethane in certain cases. For instance, fumaric ester and diazomethane yield the ester of pyrazolinic acid—



Diazomethane attacks the nitrile group, yielding derivatives of the triazole series. Thus with cyanoformic ester,[3] it gives triazole carboxylic ester :



The reaction between ketens and aliphatic diazo-compounds has not been fully studied ; but apparently diphenyl-keten acts on diphenyl-diazomethane [4] with the formation of a pyrazoline ring :



It has been pointed out in an earlier paragraph that by means of sulphuretted hydrogen some diazene derivatives can be reduced to hydrazones. In the case of dicarbonyl-substituted

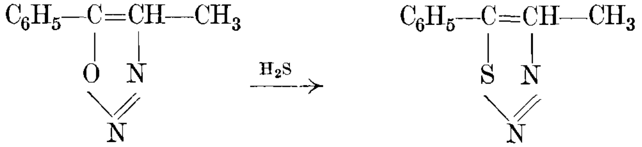
[1] Pechmann, *Ber.*, 1898, **31**, 2950.

[2] Pechmann and Seel, *Ber.*, 1899, **32**, 2294.

[3] Peratoner and Azzarello, *Gazzetta*, 1908, **38**, I. 76 ; Oliveri-Mandala, *ibid.*, 1910, **40**, I. 120.

[4] Staudinger and others, *Ber.*, 1916, **49**, 1928.

diazene derivatives (the diazo-anhydrides), however, the reaction [1] takes a different course: the sulphur atom is introduced, and the chain closes into a thiodiazole ring:



An analogous reaction leads to the formation of diphenyl-thiodiazole by the action of sulphuretted hydrogen upon phenyl-benzoyl-diazomethane.[2]

The remaining reactions leading to heterocyclic derivatives are processes of isomerization and polymerization. It has already been pointed out that the action of acids upon diazo-compounds of the aliphatic series is a disruptive one. Alkalis, on the other hand, tend to retain the nitrogen chain of the diazene group intact; and their action varies according to the concentration of the alkaline solution. Dilute alkali, for example, will hydrolyze a diazoacetic ester, yielding the corresponding metallic salt of the diazo-acid; but when stronger alkaline solutions are employed, changes are produced which are of some interest.

When diazo-acetamide and its N-substitution products are treated with weak caustic potash or barium hydroxide solutions, they are converted into triazolone [3] derivatives:

This reaction is a reversible one in which the equilibrium is influenced both by the nature of the solvent present and the constitution of the radicles introduced as substituents. For example, the parent substance yields the triazolone shown above as the stable product of the reaction, whereas in the case of the compound, $(NO_2)_2C_6H_3 . NH . CO . C(N_2) . COOEt$, the diazene form is stable and the triazolone can be obtained only in the form of an alkali salt.

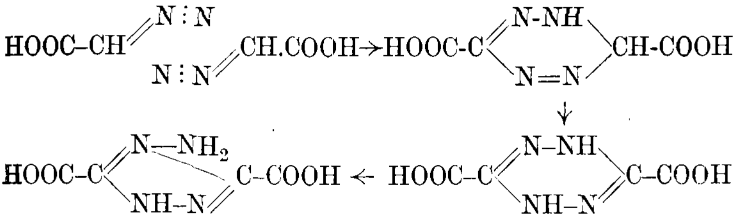
When concentrated alkaline solutions are employed, the

[1] Wolff, *Annalen*, 1902, **325**, 132.

[2] Staudinger, *Ber.*, 1916, **49**, 1884.

[3] Curtius and others, *Ber.*, 1906, **39**, 4140; 1907, **40**, 1197; 1910, **43**, 857, 862, 2441, 2447; Dimroth, *Annalen*, 1910, **373**, 336.

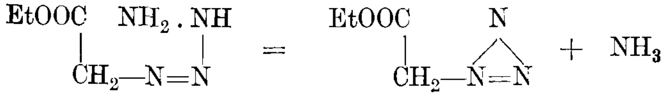
diazene derivatives undergo a different change, yielding dihydrotetrazine compounds,[1] which can undergo an even more remarkable rearrangement in which an imino-group is expelled from the ring—



As a final example of heterocyclic derivation from the aliphatic diazo-compounds, the production of a hydrazide [2] may be mentioned. When hydrazine hydrate acts upon diazoacetic ester, alcohol and ammonia are eliminated and the hydrazide of azidoacetic acid is produced. This reaction can best be explained by assuming that a tetrazene compound is formed as an intermediate stage—

$$\begin{array}{l} COOEt \\ | \\ CH:N:N \end{array} + NH_2 . NH_2 = \begin{array}{l} CO . OEt \\ | \\ CH_2 . N:N . NH . NH_2 \end{array}$$

Ammonia is then liberated during the process of ring-formation and the substituted azoimide is formed—



This azoimide then reacts with another molecule of hydrazine, the —COOEt group being converted into the hydrazide radicle, —CO . NH . NH_2, so that the final product is azidoacethydrazide.

[1] Curtius, Darapsky and Muller, *Ber.*, 1908, **41**, 3161.
[2] Curtius, Darapsky and Bockmühl, *Ber.*, **41**, 344.

CHAPTER V

THE KETENS

1. *Introductory*

THE ketens, discovered by Staudinger,[1] are derivatives of the parent substance keten itself—

$$CH_2=C=O$$

which was isolated by Wilsmore and Stewart.[2] Since the keten formula contains two hydrogen atoms, there are two main types of substitution-products; and these have been named by Staudinger *aldoketens*, R . CH : C : O, and *ketoketens*, R_2C : C : O. Regarded at first as mere chemical curiosities, the ketens gradually attracted more and more attention, partly on account of their remarkable reactivity and partly owing to the analogies, fanciful or otherwise, which were drawn between their formulæ and those of other compounds. It may be of interest here to point out one or two such analogies.

In the first place, since the keten formula contains a carbonyl radicle, it seems natural to group the ketens along with the ketones and to regard them as unsaturated ketones of a special type. Here, however, the formula resemblance is misleading; for the ketens show none of the reactions characteristic of the ketones or aldehydes. The keten carbonyl group resembles the carbonyl of a carboxyl group in its inertness with respect to phenylhydrazine, etc.

Secondly, since the ketens contain the ethylenic linkage, they might be regarded as belonging to the substituted olefines. In many respects, this structural kinship is traceable in practice ;

[1] Staudinger, *Ber.*, 1905, **38**, 1735. A full account of the ketens is given in Staudinger's pamphlet, *Die Ketene*.

[2] Wilsmore and Stewart, *Nature*, 1907, **75**, 510 ; Wilsmore, *J.*, 1907, **91**, 1938.

for the ethylenic linkage of the ketens shows all the characteristics of a genuine ethylenic bond. Some reactions of the ketens, however, go far beyond the normal activities of the olefines, as will be seen later; so it is clear that the bond C=C is influenced to a great extent by the adjacent double bond between carbon and oxygen.

Thirdly, owing to the presence of these two adjacent double bonds, it is possible to suggest analogies between the ketens and other compounds having the same bond-grouping in the structure as shown in the formulæ below:

$R_2C{=}C{=}O$	Ketens	$R_2C{=}C{=}O$	Ketens
$R_2C{=}C{=}CR_2$	Allenes	$R.N{=}C{=}O$	Isocyanates
$O{=}C{=}O$	Carbon dioxide	$R.N{=}C{=}S$	Isothiocyanates
$S{=}C{=}O$	Carbon oxysulphide	$R.N{=}C{=}N.R$	Carbodiimido-derivatives

Some of these analogies will be dealt with later in this chapter.

Fourthly, the ketens must be regarded as closely akin to the acid anhydrides on account of their reactions. At first sight, this analogy is not apparent in the formulæ; but it will become clear enough on a little consideration. It will be recalled that the dehydration of alcohol may take place in either of two ways: (1) by loss of one molecule of water from two molecules of alcohol as in ether formation; and (2) by the loss of one molecule of water from one molecule of alcohol, yielding an olefine:

$$\begin{array}{l} CH_3{-}CH_2{-}OH \\ CH_3{-}CH_2{-}OH \end{array} - H_2O = \begin{array}{l} CH_3{-}CH_2 \\ CH_3{-}CH_2 \end{array}\!\!>O$$

$$\begin{array}{cc} H & OH \\ | & | \\ CH_2{-} & CH_2 \end{array} - H_2O = CH_2{=}CH_2$$

The dehydration of acetic acid can also take place in two ways analogous to the above:

$$\begin{array}{l} CH_3{-}CO{-}OH \\ CH_3{-}CO{-}OH \end{array} - H_2O = \begin{array}{l} CH_3{-}CO \\ CH_3{-}CO \end{array}\!\!>O$$

or

$$\begin{array}{cc} H & OH \\ | & | \\ CH_2{-} & CO \end{array} - H_2O = CH_2{=}C{=}O$$

Thus the keten class may be regarded as internal anhydrides of

the corresponding acids ; and, as a matter of fact, this seems to be the best interpretation of their character. At the same time, since this dehydration process is parallel to that by which olefines are formed from alcohols, the olefinic nature of the ketens is also brought into prominence in this reaction.

2. *The Preparation of the Ketens*

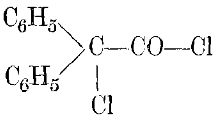
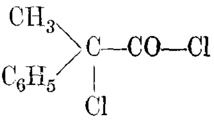
Although the ketens form a well-defined class of carbon compounds, no really general methods have yet been devised for their preparation. Apparently constitutional influences make themselves strongly felt ; and a method which goes smoothly in one case may not work at all when homologues are substituted for the parent substance. Bearing this limitation in mind, we may now deal with the various ways in which members of the keten class have been obtained.

1. *Removal of Halogen from Halogen-substituted Acyl Halides.*—This reaction, discovered by Staudinger,[1] is the nearest approach to a general method of preparation which has been discovered. Solutions of halogen-substituted acyl halides are treated with metals which remove a molecule of halogen and leave the desired keten :

$$Br . CH_2 . CO . Br \quad + \quad Zn \quad = \quad CH_2 : CO \quad + \quad ZnBr_2$$

The ease with which this reaction can be carried out is influenced by the nature of the acyl halide, by the metal chosen, and by the solvent employed.[2] For instance, bromacetyl bromide, $Br . CH_2 . CO . Br$, gives a 12 per cent. yield of keten when treated with zinc in ethereal solution ; bromacetyl chloride, $Br . CH_2 . CO . Cl$, gives a yield of only 3–4 per cent. ; whilst chloracetyl chloride, $Cl . CH_2 . CO . Cl$, hardly reacts at all under the same conditions. In some cases the influence of constitutional factors inhibits the reaction ; for zinc fails to produce any keten from trichloracetyl chloride, $Cl_3 . C . CO . Cl$. Aromatic substituents in the molecule seem to favour the reaction, since it is easy to obtain a keten from the compound (I.) while much poorer yields are given by (II.) :

[1] Staudinger, *Ber.*, 1905, **38**, 1735.
[2] Staudinger, *Die Ketene*, pp. 7 ff. (1912).

(I.)  (II.) 

Zinc is the best metal to use for the removal of the halogens. Magnesium can be employed; but in some cases it seems to favour secondary reactions which lower the yield. Silver and mercury act only slowly. As regards solvents, the best seem to be those which dissolve the metallic halide formed during the reaction. Thus anhydrous ether and acetic ester, in which zinc halides are soluble, give good results; whereas benzene and toluene make the reaction sluggish.

2. *Pyrogenic Methods.*—The simplest of these was devised by Wilsmore and Stewart.[1] An electrically-heated platinum wire is immersed in acetone or acetic anhydride *; and dehydration is thus produced:

$$(CH_3 . CO)_2O = 2CH_2 : CO + H_2O$$
$$CH_3 . CO . CH_3 = CH_2 : CO + CH_4$$

This method is, of course, most suitable in the above case, since the volatile keten distils off and is thus removed from the chance of further contact with the hot wire. This pyrogenic method has been modified by Schmidlin and Bergmann,[3] who passed acetone vapour through a tube heated in a combustion furnace and obtained keten. A careful study of the optimum conditions of this reaction has been made by Hurd and Tallyn.[4]

[1] Wilsmore and Stewart, *Nature*, 1907, **75**, 510; Wilsmore, *J.*, 1907, **91**, 1938.

* An interesting point was noted when various esters were employed in this apparatus.[2] Saturated fatty esters initially lose ethylene and yield the corresponding acids, which in their turn break up into carbon dioxide and the parent hydrocarbon of the original acid. Thus acetic ester decomposes as shown below:

$$CH_3 . COOC_2H_5 = CH_3 . COOH + C_2H_4$$
$$CH_3 . COOH = CH_4 + CO_2$$

With esters of unsaturated acids containing a conjugated system of double bonds, however, the reaction stops at the elimination of ethylene. Thus when crotonic ester, $CH_3 . CH : CH . COOC_2H_5$, is used, crotonic acid is liberated, but the reaction does not lead to loss of carbon dioxide and the production of propylene. This is a good example of the influence exerted by conjugation.

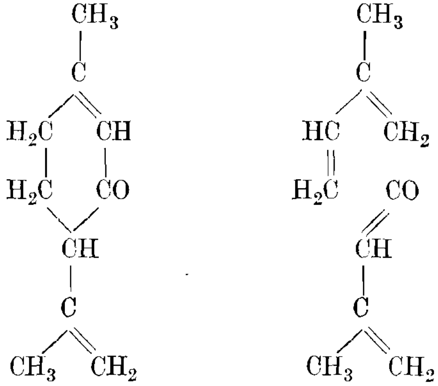
[2] Wilsmore and Stewart, *P.*, 1907, **23**, 309.

[3] Schmidlin and Bergmann, *Ber.*, 1910, **43**, 2821.

[4] Hurd and Tallyn, *J. Amer. Chem. Soc.*, 1925, **47**, 1427.

By means of a glowing platinum spiral, Klever [1] was able to break up carvone, with the production of isoprene and methyl-vinyl-keten :

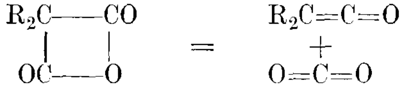
Carvone



Isoprene

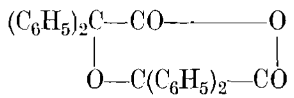
Methyl-vinyl-keten

3. *Dry Distillation.*—Some compounds break up on simple heating yielding keten derivatives. Substituted malonic anhydrides decompose as shown below :

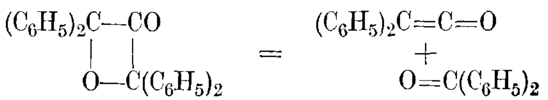


Dimethyl- and diethyl-keten have been obtained in this manner from the corresponding anhydrides ; but the reaction does not seem to be a general one.[2] A similar break up of a four-membered ring is believed to account for the production of diphenyl-keten from benzilide.[3] Benzilide is supposed to be an ether-anhydride of benzilic acid,[4] having the structure (I.). On heating, it loses carbon dioxide and yields a cyclic ketone (II.), which then breaks up into benzophenone and diphenyl-keten :

(I.)



(II.)



[1] Staudinger, *Die Ketene*, p. 29 (1912).
[2] Staudinger and Ott, *Ber.*, 1908, **41**, 2208, 3829.
[3] Staudinger, *Ber.*, 1911, **44**, 543.
[4] Stollé, *Ber.*, 1910, **43**, 2473.

By distilling a mixture of malonic acid and phosphorus pentoxide, Diels [1] obtained carbon suboxide, which belongs to the keten class :

$$HO.CO.CH_2.CO.OH = O:C:C:C:O + 2H_2O$$

4. *From Diazene Derivatives.*—It has been pointed out in the previous chapter that ketodiazene compounds on heating yield ketens.[2] Phenyl-benzoyl-diazomethane in this way gives rise to diphenyl-keten. Another reaction of the diazene series is of theoretical interest, though in practice the yields are poor and the process is applicable only in the case of diazomethane. When this substance is heated with carbon monoxide,[3] nitrogen is eliminated and the remaining groups combine :

$$N{\equiv}N:CH_2 + CO = N_2 + CH_2:CO$$

It is suggested that the liberation of nitrogen leaves a free methylene radicle, which then unites with the molecule of carbon monoxide.

3. *Some Reactions of the Ketens*

It has already been pointed out that although the ketens contain the carbonyl radicle, this group shows no reactive power ; and the activity of the ketens appears to be concentrated in the ethylenic linkage. It will suffice here to give some typical reactions of the keten class ; and from these examples it will be clear that the ethylenic linkage in the keten molecule is possessed of properties not normally observed in olefinic derivatives, since it has the power of attacking some reagents which are left unaffected by simple olefines.

1. *Reactions yielding Open-chain Derivatives of Acids.*—The halogens attack the ethylenic linkage in the normal manner and yield halides of halogen-substituted acids :

$$CH_2:CO + Br_2 = Br.CH_2.CO.Br$$

The remarkable inertness of the carbonyl group of the ketens is brought out when the action of keten on phosphorus penta-

[1] Diels and others, *Ber.*, 1906, **39**, 689 ff. ; 1907, **43**, 2821.
[2] Schroeter, *Ber.*, 1909, **42**, 2346.
[3] Staudinger and Kupfer, *Ber.*, 1912, **45**, 504 ; Staudinger, *ibid.*, 1916, **49**, 1888, 1937.

chloride is examined. In that case, the keten abstracts two halogen atoms from the pentachloride :

$$CH_2:CO + PCl_5 = Cl.CH_2.CO.Cl + PCl_3$$

Turning next to the reactions between ketens and compounds containing replaceable hydrogen atoms, it is found that all these substances behave analogously. The following equations will show the parallelism between the various types :

$$\begin{array}{lllll} CH_2:CO & + & H.Cl & = & CH_3.CO.Cl \\ CH_2:CO & + & H.OH & = & CH_3.CO.OH \\ CH_2:CO & + & H.OEt & = & CH_3.CO.OEt \\ CH_2:CO & + & H.NH_2 & = & CH_3.CO.NH_2 \\ CH_2:CO & + & H.NH.R & = & CH_3.CO.NH.R \end{array}$$

It is obvious from these formulæ that the hydrogen atom attaches itself to the methylene carbon, whilst the remainder of the molecule becomes joined to the carbon atom carrying the oxygen.

Organic acids react with ketens in a normal manner, yielding anhydrides.[1]

$$(C_6H_5)_2C:CO + HO.CO.C_6H_5 = (C_6H_5)_2CH.CO.O.CO.C_6H_5$$

The chlorides of monocarboxylic acids appear to have no action on ketens ; but phosgene and oxalyl chloride react as might be anticipated, by addition to the ethylenic linkage :

$$(C_6H_5)_2C:C:O + COCl_2 = \begin{array}{l}(C_6H_5)_2C{-}COCl \\ \qquad\quad\;\; | \\ \qquad\quad\; COCl\end{array}$$

$$(C_6H_5)_2C:C:O + Cl.CO.CO.Cl = \begin{array}{l}(C_6H_5)_2C{-}COCl \\ \qquad\quad\;\; | \\ \qquad\quad\; CO.COCl\end{array}$$

Two apparently abnormal cases may be mentioned here. When keten reacts with hydrocyanic acid [2] the reaction product is made up of two molecules of keten and one molecule of hydrocyanic acid. It is unstable, and with water it decomposes into two molecules of acetic acid and one of hydrocyanic acid. Deakin and Wilsmore formulate the reactions as follows :

$$\begin{array}{rcl} CH_2:C:O + H.CN & = & CH_2:C(CN).OH \\ CH_2:C(CN).OH + CH_2:C:O & = & CH_2:C(CN).O.CO.CH_3 \\ CH_2:C(CN).O.CO.CH_3 + 2H_2O & = & 2CH_3.COOH + HCN \end{array}$$

[1] Staudinger, *Annalen*, 1907, 356, 79.
[2] Deakin and Wilsmore, *J.*, 1910, **97**, 1969.

which seems to be the only satisfactory way of expressing this very peculiar series of changes.

In the case of the reaction between hydrogen sulphide and keten, the production of thioacetic acid might have been expected; but in practice [1] it is found that two molecules of keten react with one molecule of hydrogen sulphide, yielding thioacetic anhydride:

$$2CH_2:CO + H_2S = (CH_3.CO)_2S$$

2. *Autoxidation.*[2]—When oxygen is passed into an ethereal solution of dimethyl-keten cooled to $-20°$ C., a white amorphous powder is formed, which is termed the primary autoxidation product or moloxide.* When dried, the compound is liable to explode violently and spontaneously. In ethereal suspension, decomposition only occurs on warming; and the material gradually decomposes, forming acetone. These changes may be formulated thus:

$$\begin{array}{c} (CH_3)_2C{=}CO \\ + \\ O{=}O \end{array} = \begin{array}{c} (CH_3)_2C{-}CO \\ |\quad\ | \\ O{-}O \end{array} = \begin{array}{c} (CH_3)_2C \\ \| \\ O \end{array} + \begin{array}{c} CO \\ \| \\ O \end{array}$$

The peroxide nature of these primary autoxidation products is established by their action on potassium iodide solutions, which is the same as that of any ordinary peroxide.

This peroxide formation takes place only with ketoketens; aldoketens do not yield moloxides. It is further influenced by the constitution of the ketoketen, since the introduction of aromatic nuclei into the molecule tends to make the peroxide less stable. The rate of decomposition becomes greater than the velocity of the moloxide's formation.

Secondary autoxidation products of the ketens are the same as those obtained by acting on the ketens with normal oxidizing agents. Keten, for example, yields acetone and carbon dioxide.

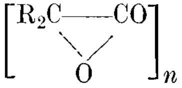
In addition to these, a third type of compound is obtained

[1] Chick and Wilsmore, *P.*, 1909, **24**, 77.

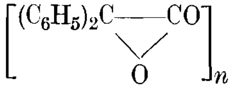
[2] Staudinger, *Die Ketene*, pp. 49 ff. (1912); see also for autoxidation in general, Engler and Weissberg, *Kritische Studien über die Vorgänge der Autoxydation* (1904).

* So called because they are formed from one molecule of oxygen acting on one molecule of a keten.

during autoxidation—the so-called keten oxides. These have compositions corresponding to—



and they are prepared by passing oxygen through ethereal solutions of ketens at ordinary temperatures. On heating with water, diphenyl-keten oxide yields benzilic acid—

 $+ \; nH_2O \; = \; n(C_6H_5)_2C(OH) \,.\, COOH$

Rather unexpectedly, the action of methyl alcohol on diphenyl-keten oxide produces diphenyl-methoxy-acetic acid (I.) while aniline gives a quantitative yield of anilido-diphenylacetic acid (II.).

$$\text{(I.)}\quad \begin{array}{l}(C_6H_5)_2C\text{—}COOH\\ \qquad\quad |\\ \qquad\; OCH_3\end{array} \qquad\qquad \text{(II.)}\quad \begin{array}{l}(C_6H_5)_2C\text{—}COOH\\ \qquad\quad |\\ \qquad\; NH \,.\, C_6H_5\end{array}$$

In this last case, the production of the anilide of benzilic acid is what might have been expected to occur.

3. *The Grignard Reaction.*—Only one or two applications of the Grignard reaction to ketens have been made. Keten,[1] when treated with methyl-magnesium iodide, produces acetone. This reaction may be regarded as due to an attack on the carbonyl radicle such as is usually found with ketonic compounds and the Grignard reagent; or it may be brought into line with the rest of the keten reactions by assuming that the Grignard reagent attaches itself to the ethylenic bond, as shown below:

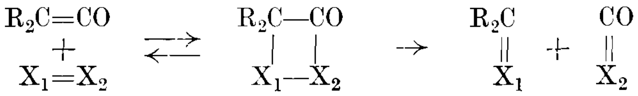
$$CH_2 : CO \; + \; CH_3 \,.\, Mg \,.\, I \; = \; I \,.\, Mg \,.\, CH_2 \,.\, CO \,.\, CH_3$$
$$I \,.\, Mg \,.\, CH_2 \,.\, CO \,.\, CH_3 + H_2O = CH_3 \,.\, CO \,.\, CH_3 + I \,.\, Mg \,.\, OH$$

Diphenyl-keten, when treated with phenyl-magnesium bromide, yields triphenyl-vinyl alcohol, $(C_6H_5)_2C : C(OH) \,.\, C_6H_5$.

4. *Addition of Ketens to Double Bonds.*—The extraordinary activity of the ethylenic bond in the keten molecule is manifested by the readiness with which the ketens react with many unsaturated substances. As a result of these reactions, four-membered rings appear to be formed in the majority of cases.

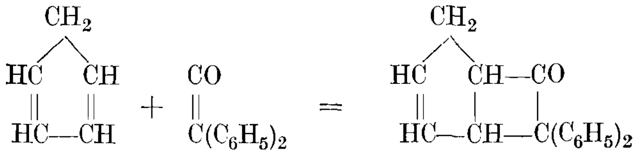
[1] Deakin and Wilsmore, *J.*, 1910, **97**, 1968.

Some of these four-membered rings are marked by great instability; and the compounds containing them tend to decompose either with the regeneration of the original materials or else with the formation of fresh substances according to the scheme below:



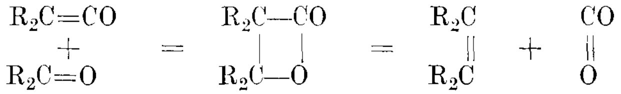
The stability of the four-membered ring is largely governed by the nature of the compound with which the keten unites; but no general rule can be traced which would show that easily-formed compounds are readily decomposed or that rings which are hard to form are stable. One or two examples may now be given to show the nature of the compounds produced by the action of ketens on unsaturated molecules. The reaction between ketens and pyridine derivatives will be dealt with in the next section, so they are omitted from the present survey.

Ketens react with the ethylenic bond only in special cases.[1] No reaction occurs between diphenyl-keten and the following olefinic derivatives: fumaric ester, cinnamic ester, benzal-malonic ester, styrol, or diphenyl-ethylene. This last substance reacts with diphenyl-keten at high temperatures, however, but the product seems to be a hexahydrobenzene derivative and not a tetramethylene compound. On the other hand, compounds containing the cyclopentadiene ring, such as dimethyl-fulvene, phenyl-methyl-fulvene, and cyclopentadiene itself, unite with diphenyl-keten. For example, cyclopentadiene yields a crystalline product apparently having the structure shown below. On heating to a high temperature, this substance breaks up, regenerating the two starting-materials.



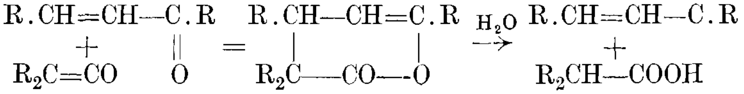
With aromatic ketones and aldehydes, the ketens react to form β-lactones which, being extremely unstable, decompose spontaneously as shown in the following formulæ:

[1] Staudinger, *Die Ketene*, p. 59 (1912).

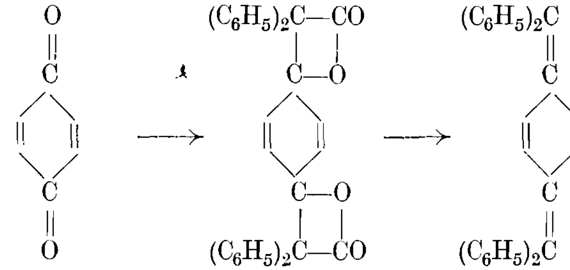


The addition of the keten takes place only when the temperature is raised ; and under these conditions the lactone breaks up as soon as it is formed. In the case of diphenyl-keten and dimethyl-amino-benzaldehyde, however, the lactone has actually been isolated.[1] Pyrone [2] yields with diphenyl-keten a pyrane derivative, the group $(C_6H_5)_2C=$ taking the place of the carbonyl oxygen atom.

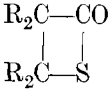
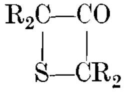
When the α-unsaturated ketones were examined, it was found that instead of yielding four-membered rings, they gave rise to six-membered cyclic systems, which on hydrolysis produced substituted acetic acids and the original ketones :



Quinone, on the other hand, yields the normal β-lactone, which can be broken up to give the tetra-phenyl derivative shown below :



When treated with ketens, the thioketones react more easily than ordinary ketones. The reaction products may be either β-thiolactones of the type (I.) or cyclic sulphides of the form (II.).

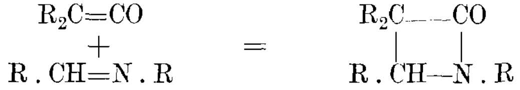
(I.)  (II.) 

Compounds of type (I.) are believed to exist if carbon oxysulphide is liberated on heating the substances. Compounds of

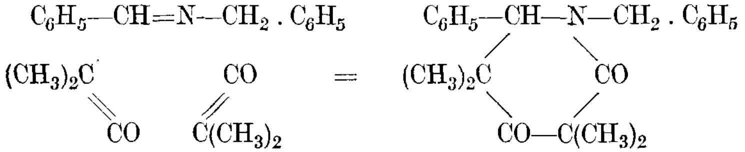
[1] Staudinger, *Die Ketene*, p. 61 (1912).
[2] Staudinger, *Ber.*, 1909, **42**, 4249.

type (II.), on the other hand, break up into the original materials from which they were synthesized. Thioesters, thioamides, and thio-urea derivatives do not react with ketens.

Turning next to compounds containing the group =C : N—, it is found that ketens react readily with Schiff's bases to form β-lactams:

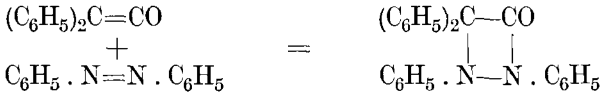


These lactams are very stable compounds, wherein they differ from the analogous lactones derived from ketones. They decompose only at high temperatures, yielding either the original substances or else phenyl isocyanate and an ethylene derivative. Sometimes, as in the reaction between dimethyl-keten and benzal-benzylamine, a six-membered ring is produced :

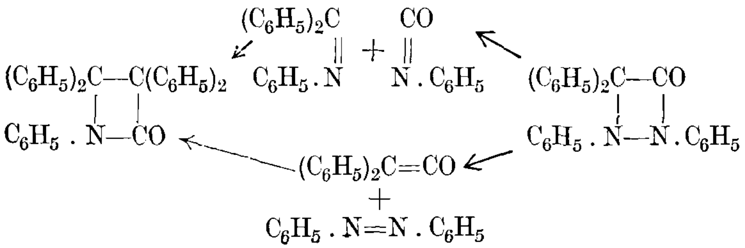


It may be mentioned that ketens do not react with phenylhydrazones, oxime ethers, benzanilide-imido-chloride or phenyl isocyanate, although these compounds all contain the double bonds between carbon and nitrogen atoms.

One of the most remarkable reactions in this field is found in the interaction of ketens with compounds containing the azo-group, —N : N—. Here, as in other cases, a four-membered ring is produced :



When heated, this substance breaks down simultaneously along two different lines :



It can be seen from the formulæ that the Schiff's base and the keten, formed by the two different types of decomposition, unite in the final stage to yield a fresh four-membered ring, different from the original one.

This survey of the action of ketens upon double bonds may be closed with a reference to the behaviour of the nitroso-group. Diphenyl-keten acts upon nitrosobenzene, yielding a compound which is not analogous to the β-lactones and lactams :

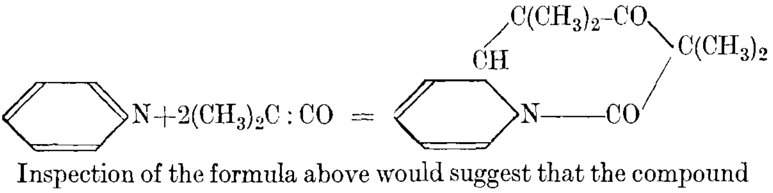
$$\begin{array}{c} (C_6H_5)_2C{=}CO \\ + \\ O{=}N\,.\,C_6H_5 \end{array} \quad = \quad \begin{array}{l} (C_6H_5)_2C{-}CO \\ \quad\;\; | \quad\; | \\ \quad\;\; O{-}N\,.\,C_6H_5 \end{array}$$

This substance, on heating, decomposes with almost explosive violence into benzophenone and phenyl isocyanate. Substituted nitroso-compounds react differently from the parent substance. They yield compounds, analogous to the β-lactones, from which on heating, Schiff's bases are liberated—

$$\begin{array}{c} R_2C{=}CO \\ + \\ R\,.\,N{=}O \end{array} \longrightarrow \begin{array}{l} R_2C{-}CO \\ \;\;\;\; | \quad\; | \\ R\,.\,N{-}O \end{array} \longrightarrow \begin{array}{c} R_2C \\ \| \\ R\,.\,N \end{array} + \begin{array}{c} .CO \\ \| \\ O \end{array}$$

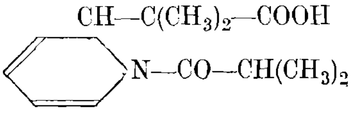
These Schiff's bases may then react with a further molecule of the keten to yield the usual β-lactam.

5. *Keten-bases and Ketenium-compound Formation.*—When ketoketens act upon pyridine and its derivatives, the normal keten reaction with the group —CH : N— fails ; and instead, two molecules of the ketoketen interact with one molecule of the base, yielding a peculiar compound which is termed a *keten-base :*



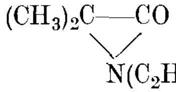
Inspection of the formula above would suggest that the compound is simultaneously a derivative of dihydropyridine and a diketo-piperidine.

On treatment with acids or alkali, however, these keten-bases open up, yielding dihydro-pyridine-substituted acids of the type shown below :

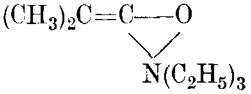


and on heating to a high temperature, these substances in turn decompose, yielding the original base and the anhydride of an acid, which in the above case would be $((CH_3)_2CH . CO)_2O$.

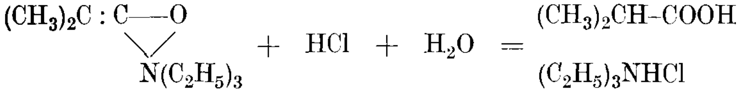
When an aliphatic tertiary base is heated with an acid halide, a molecule of halogen hydride is eliminated, and the residual material has a composition corresponding to one molecule of the tertiary base plus one molecule of a keten. For example, when triethylamine is heated with isobutyryl chloride, a substance is produced which appears to have one of the constitutions :



or



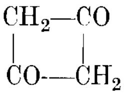
These *ketenium compounds* [1] are remarkably stable, being attacked even by concentrated hydrochloric acid only at high temperatures :



6. *Polymerization.*—The activity of the ethylenic linkage in the ketens makes itself specially manifest in the ease with which these substances polymerize. Keten itself is polymerized at ordinary temperatures.[2] The aldoketens polymerize so readily, even in dilute solution, that they cannot be obtained in a pure state ; in the ketoketen series also polymerization is rapid, being quickest in the case of dimethyl-keten and least rapid in the case of diphenylene-keten.[3]

According to the evidence in other cases of polymerization, such as those of acetaldehyde and cyanic acid, it might be expected that three molecules of keten would unite to form a six-membered ring ; so that keten itself would yield phloroglucinol as a polymer. In practice, however, only two molecules of keten unite together. The product of this reaction could be formulated in either of the following ways :

$CH_3 . CO . CH : C : O$ (I.)



(II.)

[1] Wedekind and Miller, *Ber.*, 1909, **42**, 1269.

[2] Wilsmore and Stewart, *Nature*, 1907, **75**, 510 ; Chick and Wilsmore, *J.*, 1908, **93**, 946.

[3] Staudinger, *Die Ketene*, p. 38 (1912).

Wilsmore and Chick[1] supplied the evidence which enables a decision to be made between these two formula. When bromine acts on the polymer, the compound γ-bromo-acetoacetyl bromide, $Br . CH_2 . CO . CH_2 . CO . Br$ is formed, which is evidently produced by a rupture of the tetramethylene ring, since the open-chain formula would lead to $CH_3 . CO . CHBr . CO . Br$. Further evidence is to be found in the fact that the polymer is not readily attacked by alcohol or phenols ; for if it had the keten structure it should react immediately with these.

The polymer, diketen, is readily attacked by water, aniline, and phenylhydrazine, the products being respectively acetoacetic acid, acetoacetanilide, and acetoacetic-phenylhydrazone-phenylhydrazide. This last reaction shows that one carbonyl group in diketen acts like a ketonic one, whilst the other carbonyl radicle behaves like the carbonyl of a carboxyl group, which suggests that the tetramethylene ring opens during the course of the reaction, so as to generate acetoacetic acid.

Diketen can be distilled intact; but some of its substitution products can be broken down by heat into the ketens from which they were derived. Thus when the polymer of dimethyl-keten is vaporized over a heated platinum wire, it is decomposed again into dimethyl-keten.[2]

4. *Some Typical Ketens*

In the foregoing sections, a survey has been made of the preparation and the chemical properties of the keten class ; and it seems advisable to add here a short account of one or two individual members of the group. For this purpose, the following have been selected : keten, dimethyl-keten, the ethyl ester of ethyl-keten-carboxylic acid, diphenyl-keten, and carbon suboxide.

Keten,[3] $CH_2 : C : O$, is a colourless gas with an extremely penetrating smell, affecting the mucous membrane. At —56° C.

[1] Wilsmore and Chick, *J.*, 1908, **97**, 1978.

[2] Staudinger, *Die Ketene*, p. 23 (1912) ; see also Staudinger and Ruzicka, *Annalen*, 1911, 380, 302.

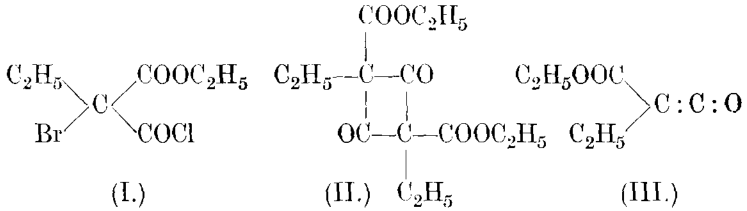
[3] Wilsmore and Stewart, *Nature*, 1907, **75**, 510 ; Wilsmore, *J.*, 1907, **91**, 1938 ; Chick and Wilsmore, *ibid.*, 1908, **93**, 946 ; 1910, **97**, 1978 ; Deakin and Wilsmore, *ibid.*, 1968 ; Stewart and Wilsmore, *Ber.*, 1908, **41**, 1025 ; Staudinger and Klever, *ibid.*, 594, 1516 ; Schmidlin and Bergmann, *ibid.*, 1910, **43**, 2821.

it condenses to a colourless liquid which freezes to a solid at —151° C. It is very unstable, and can be preserved unaltered only at temperatures well below its boiling-point. Even at zero, it rapidly polymerizes to diketen, heat being evolved during the reaction. The diketen so formed boils at 126°–127° C. Keten is not rapidly attacked by dry oxygen, but combines instantaneously with water, alcohols, primary amines, and ammonia. It shows none of the usual keten reactions with unsaturated compounds and forms no keten-base with quinoline. In presence of pyridine, it (and diketen) polymerizes to dehydracetic acid, though the yield is small. At high temperatures, keten is decomposed into ethylene and carbon monoxide.

Dimethyl-keten,[1] $(CH_3)_2C:C:O$, is a pale-yellow liquid boiling at 34° C. and having the usual characteristic odour of the ketens. At —98° C. it solidifies to a yellowish mass. Its vapour also is slightly coloured. It is prepared by the action of zinc upon bromo-isobutyryl bromide in ethereal solution. It is very unstable, polymerizing rapidly to tetramethyl-diketo-tetramethylene, a solid of m.p. 113–4° C., having a camphor-like odour.[2] Dimethyl-keten differs from keten itself in being sensitive to oxygen, which acts on the dimethyl-compound with the production of an explosive peroxide. A further difference is found in the fact that dimethyl-keten forms keten-bases with quinoline, etc., and combines normally with Schiff's bases. It reacts with nitrosobenzene but fails to attack azobenzene. At high temperatures, it breaks up into carbon monoxide and propylene or tetramethyl-ethylene.

Ethyl-keten-carboxylic Ester,[3] $EtOOC.C(C_2H_5):C:CO$, is a colourless liquid, fuming in air, and possessing a suffocating odour. It boils at 48° C. and solidifies at —58° C. It is very unstable and soon changes to a thicker liquid, which appears to be diethyl-diketo-tetramethylene-dicarboxylic ester. It is prepared by the action of zinc upon the ester-chloride of ethylbromomalonic acid (I.), which produces the tetramethylene polymer (II.), from which the desired keten (III.) is obtained by distillation in vacuo at 180°–200° C. and cooling the receiver to —80° C.

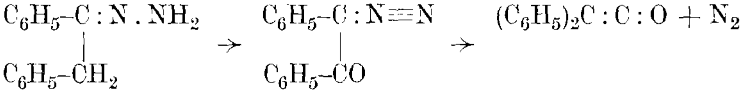
1 Staudinger and Bereza, *Ber.*, 1908, **41**, 3426.
2 Staudinger, *Helv. Chim. Acta*, 1925, **8**, 306.
3 Staudinger and Bereza, *Ber.*, 1909, **42**, 4908.



(I.) (II.) (III.)

With water, the keten yields ethyl-malonic acid. It is not subject to autoxidation, nor does it react with quinoline, though it combines with benzylidene-aniline in the normal manner.

Diphenyl-keten,[1] $(C_6H_5)_2C : C : O$, was the first representative of the keten class to be discovered. It was obtained by the action of zinc upon the chloride of chloro-diphenyl-acetic acid, but it is now more readily prepared from benzyl-hydrazone, by oxidizing this to a diazene derivative by means of mercuric oxide and then breaking up the diazene compound by distillation in vacuo, during which process an isomeric change takes place :



Diphenyl-keten is an orange-coloured liquid of m.p. 146° C. at 12 mm. pressure. In a freezing-mixture it changes to yellow crystals. It is much more stable than dimethyl-keten, polymerizing only very slowly at ordinary temperatures. It gives all the normal keten reactions. On heating to 700° C. it breaks up into carbon monoxide and fluorene. It is sensitive to oxygen, yielding very readily benzophenone, carbon dioxide, and a mixture of keten oxides.

Carbon suboxide,[2] O : C : C : C : O, is an example of a complex keten. It is a colourless gas with characteristic odour and disagreeable physiological effects. At —7° C. it condenses to a colourless liquid which solidifies at —107° C. to colourless crystals. It is very unstable, though not quite so readily polymerized as keten. It can be obtained by the action of phosphorus pentoxide upon malonic ester or malonic acid, or by heating a mixed malono-formic anhydride, or by the action of zinc on dibromo-malonyl chloride, or by the interaction of

[1] Staudinger, *Ber.*, 1905, **38**, 1735 ; *Annalen*, 1907, **351**, 51.

[2] Diels and others, *Ber.*, 1906, **39**, 689 ; 1907, **40**, 355 ; 1908, **41**, 3426 ; *Z. angew. Chem.*, 1926, **39**, 1025 ; Staudinger and Bereza, *ibid.*, 1908, **41**, 4461.

benzoyl chloride and silver malonate. The best yield is obtained by the normal method with zinc. When treated with water, alcohol, or amines, carbon suboxide yields malonic acid or its derivatives. Acetic and formic acids react with it, producing mixed anhydrides of malonic acid. It fails to show the keten reactions with Schiff's bases; and it is not attacked by oxygen like other ketens. On heating to high temperatures, it is decomposed into carbon and carbon monoxide.

5. *Conclusion*

In the introductory section of this chapter, mention was made of certain analogies between the ketens and the members of other classes of compounds; and before leaving the subject, it seems desirable to say a few words on the point.[1]

The most obvious analogy in formulæ is to be found in the case of the isocyanic esters, R . N : C : O, on the one hand, and the ketens, R . CH : C : O, on the other. In both series, the carbonyl radicle is attached to the remainder of the molecule by a double bond, so that a certain similarity in reaction might be expected in the two classes; while at the same time the chemical difference between the group CH and the nitrogen atom must introduce variations which will prevent an exact parallelism between the cases.

So far as negative evidence goes, the two sets of substances agree in properties. Like the aldoketens, the isocyanates are not subject to autoxidation; they do not form four-membered rings; and they fail to react with pyridine and quinoline.

On the positive side also, resemblances can be detected. Thus the synthesis of ketens by removal of halogen from bromoacyl chlorides finds its parallel in the preparation of methyl isocyanate by the removal of hydrochloric acid from methyl carbaminic chloride by means of lime:

$$CH_3\text{—}NH\text{—}CO\text{—}Cl \quad - \quad HCl \quad = \quad CH_3\text{—}N : C : O$$

The Diels' method of preparing carbon suboxide finds its analogue in the formation of phenyl isocyanate by the action of phosphorus pentoxide upon phenyl-urethane:

$$C_6H_5\text{—}NH\text{—}CO\text{—}OC_2H_5 \quad - \quad C_2H_5OH \quad = \quad C_6H_5\text{—}N : C : O$$

[1] Further examples are to be found in Staudinger's *Die Ketene* (1912).

The action of alcohols upon ketens and the alkyl isocyanates shows that in both cases the addition takes place at the double bond next the carbonyl group :

$$\begin{array}{lcl} CH_3—CH:C:O + EtOH & = & CH_3—CH_2—CO—OEt \\ CH_3—N:C:O + EtOH & = & CH_3—NH—CO—OEt \end{array}$$

With ammonia, both groups react similarly :

$$\begin{array}{lcl} CH_3—CH:C:O + NH_3 & = & CH_3—CH_2—CO—NH_2 \\ CH_3—N:C:O + NH_3 & = & CH_3—NH—CO—NH_2 \end{array}$$

The actions of water upon the ketens and alkyl isocyanates are obviously alike ; but a difference is introduced owing to the instability of the carbaminic acids formed from the isocyanates, since these acids at once break up, with the loss of carbon dioxide and the formation of an amine :

$$\begin{array}{l} CH_3\text{-}CH:C:O + H_2O = CH_3—CH_2—CO—OH \\ CH_3—N:C:O + H_2O = CH_3—NH—CO—OH = CH_3.NH_2 + CO_2 \end{array}$$

Somewhat similar parallelisms can be traced between the ketens and the alkyl thiocyanates, but it is unnecessary to deal with them here.

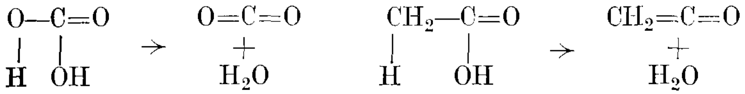
Even in the capacity for polymerization the ketens and the isocyanic esters show a certain resemblance ; for both have a marked tendency to polymerize with the evolution of heat. In the case of most isocyanic esters, the parallel stops here, since they yield trimeric polymers whereas the ketens yield dimeric products ; but phenyl isocyanate [1] under certain conditions actually yields a four-membered ring which breaks down on heating, just like the corresponding keten derivative :

$$2C_6H_5.N:C:O \rightleftharpoons \begin{array}{l} C_6H_5—N—CO \\ \quad\quad\;\; | \quad\; | \\ \quad\quad\; CO—N—C_6H_5 \end{array}$$

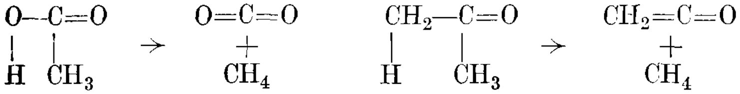
$$2C_6H_5.CH:C:O \rightleftharpoons \begin{array}{l} C_6H_5—CH—CO \\ \quad\quad\;\; | \quad\;\; | \\ \quad\quad\; CO—CH—C_6H_5 \end{array}$$

Even carbon dioxide and carbon disulphide appear to have certain analogies with the ketens in virtue of the twin double bonds in their molecules. Thus the liberation of carbon dioxide from carbonic acid bears more than a surface resemblance to the production of keten from acetic acid :

[1] Hofmann, *Ber.*, 1871, **4**, 246 ; Snape, *J.*, 1886, **49**, 254.



and the preparation of keten from acetone by the Wilsmore-Stewart pyrogenic method finds a parallel in the ordinary preparation of methane from acetic acid :



The parallelism in the case of carbon disulphide can be traced in reactions such as the formation of xanthogenates with alcohols, the production of salts of alkyl-dithiocarbaminic acids by the action of amines, etc.

The analogy between the aliphatic diazo-compounds and the ketens is not nearly so close as those which have just been indicated ; but it seems worth mentioning. In most cases an exact parallelism is not to be expected, owing to the ease with which nitrogen is liberated from the diazene derivatives as a result of reactions. The manner in which both ketens and diazene derivatives attack certain double bonds is, however, enough to suggest some similarity between the two types.

CHAPTER VI

THE POLYKETIDES AND THEIR ALLIES

1. *The Organic Chemistry of Nature*

As every chemist knows, modern synthetic work on the carbon compounds took its rise almost exactly a century ago with Wöhler's conversion of ammonium cyanate into urea. It is not without interest to glance backward and to inquire what changes that discovery inaugurated. The most obvious result of Wöhler's work is seen in the way in which the older natural products have become lost in the vast accumulation of synthetic substances which have poured out of chemical laboratories during the last century. The sequel to this has been a rigid systematization of the subject according to certain intellectual standards ; and this systematization has become more and more minute as the years went by. Even the most cursory comparison between Gmelin's *Handbuch der organischen Chemie*, published in the middle of last century, and Meyer and Jacobson's monumental *Lehrbuch*, will bring to light the giant strides which have been made in the direction of arranging the material into definite classes.

Every gain has its corresponding loss, however ; and in the development of this beautiful system, something has undoubtedly been allowed to drop out of sight. The original subjects of the old organic chemistry have been wrenched apart from one another, and each has been dropped into its appropriate place in the new system of the carbon compounds ; so that at the present day it is difficult to obtain from the ordinary systematic text-book any clear idea of the natural products as a group. They have now become so much a part of the system that in many cases the ordinary organic chemist would have difficulty in saying off-hand whether a substance is a product of nature or of the laboratory.

And yet, undoubtedly, the subjects of the earlier organic chemistry have one general characteristic which is implicit in their origin: all of them are compounds which can be produced from simple materials within a very restricted range of temperature. This is self-evident; for the plants are obviously the ultimate source of all vital products, and no plant or animal can survive outside a very limited zone in the temperature scale. Thus the true "organic" compounds are a group of materials synthesized in the course of reactions which must proceed at ordinary temperatures; and this recalls the fact that only a limited number of such reactions are possible in practice. In laboratory work, actions of this type are comparatively rare: esterification, etherification, amide-formation, condensation, hydrolysis, the opening and closing of rings, and one or two other reactions, make up the available list; and it is evident that in most cases the underlying process is an addition or removal of water during the reaction. Some of these "vital" processes are exactly paralleled in the laboratory; others can be carried out at temperatures higher than plants could bear; but some of them, which are normally carried out on the largest scale in the vegetable world, are without parallel in our synthetic methods. In these cases, the plant apparently utilizes catalysts which have not yet found their way into "practical" chemistry.

The limitations imposed on chemical changes in the living plants and animals find their reflection in the compounds formed by vital action. The most cursory examination of biochemical products brings another point to light. Taking the principal classes of natural compounds as examples, it is found that Nature works along very definite and restricted lines, producing her results mainly by the application of a general reaction to closely allied materials. Thus, as will be seen in a later chapter,* the proteins are all built up on the same principle by the general reaction of amide-formation. The flower pigments have a single common skeleton which underlies tints as varied as those of the blue corn-flower and the scarlet pelargonium; so that, despite their remarkable variety, these colouring matters are all evidently built up on analogous lines. The open-chain, cyclic, and dicyclic terpenes have structural relationships which point to similar origins for the members of the whole group. The sugars,

* See Chapter XI.

the celluloses, the fruit acids, and the vegetable esters of the fatty series have such obvious inter-relationships that it is unnecessary to stress their kinship with each other. When the nitrogenous heterocyclic compounds come under consideration, the same curious combination of monotony in method with variety in detail is detectable. The pyridine ring forms part of the constitution of all the principal alkaloids ; so that the building up of this structure is evidently one of the fundamental processes in the natural syntheses of these materials.

One of the most curious examples in this branch is to be found by comparing chlorophyll, the green colouring matter of plants, with hæmine, the red colouring matter of animal blood. Here are two extremely complex compounds performing functions which are not parallel but rather are complementary ; and yet from what we can surmise as to their constitutions, they seem to be constructed on the basis of similar skeletons. It would seem as though the original plants had developed chlorophyll as the best machinery for respiration ; and that, when the first animals developed from these plants, there was no attempt to devise a special type of compound for use in the blood. Instead, the original chlorophyll skeleton was perpetuated ; and only such modifications were introduced as would suffice to fit it for its fresh purpose.

Now the defect of our modern systematization of carbon chemistry is that it thrusts matters of this kind into the background. They are not only lost sight of in the mass of synthetic data ; but the rigid classification of most exhaustive works on organic chemistry makes it hard to bring together the vital materials and segregate them from the purely laboratory products. It is only by consulting special treatises [1] that a conspectus of this field can be obtained.

When the chemistry of plant products is looked at from the "organic" standpoint, four main classes at once attract attention : the carbohydrates, the pyrone group, the pyridine compounds, and the benzene series, including derivatives containing reduced benzene rings. On the surface, these classes appear unrelated to each other ; but in actual fact the kinship among them can be traced in practice. The remaining sections of this

[1] See Haas and Hill, *Chemistry of Plant Products*, or Trier, *Chemie der Pflanzenstoffe*.

chapter will be devoted to bringing to light some of these associations and indicating how it is possible to pass from one series to another by means of simple reactions.

2. *The Polyketides*

In the foregoing chapter, attention was directed to the properties of keten, $CH_2 : C : O$; but this compound must now be considered from a fresh standpoint. Keten's most salient characteristics are its faculty of polymerization and its power of taking up a molecule of water in order to form an acid. Now, theoretically keten could yield a series of polymers, each of which could take up a molecule of water, so that the following substances would be obtained :

$H.(CH_2.CO).OH$	=	Acetic acid	$CH_3.COOH$
$H.(CH_2.CO)_2.OH$	=	Acetoacetic acid	$CH_3.CO.CH_2.COOH$
$H.(CH_2.CO)_3.OH$	=	Triacetic acid	$CH_3.CO.CH_2.CO.CH_2.COOH$
$H.(CH_2.CO)_4.OH$	=	Tetracetic acid	$CH_3.CO.CH_2.CO.CH_2.CO.CH_2.COOH$
		or	$CH_3.CO.CH_2.CO.CH.COOH$
			|
			$CH_3.CO$

Acetic acid, the simplest member of the series, is a stable substance. Acetoacetic acid can be obtained ; but it readily decomposes into carbon dioxide and acetone. Triacetic acid has never been isolated, owing to the readiness with which it forms a lactone ; but even this lactone breaks up easily with the formation of carbon dioxide and acetylacetone. Finally, tetracetic acid also is unknown in the free state, since it spontaneously yields dehydracetic acid. These facts show that compounds containing chains of ketenic groups are characterized by an instability which increases with the number of carbonyl radicles in the molecule.

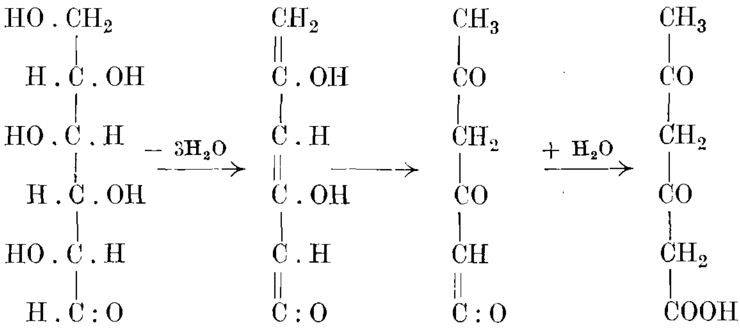
Inspection will show that the general formula of the above series is $H.(CH_2.CO)_n.OH$. The compounds therefore furnish a certain parallel to the simple polypeptides * having the general formula $H.(NH.CH_2.CO)_n.OH$; and Collie [1] proposed the analogous name *polyketides* to describe them. A polyketide can be defined as a compound obtained by uniting together a number of keten groups and then saturating the remaining affinities by means of one molecule of water. Acetic

* See Chapter XI.

[1] Collie, *P.*, 1907, **23**, 230.

acid is termed a *monoketide ;* acetoacetic acid is a *diketide,* and so on.

Theoretically, a close relationship exists between the polyketides and the carbohydrates,[1] as can be seen by inspection of the formulæ below. The removal of three molecules of water from a hexose, followed by rearrangement of the keto-enolic groupings and the addition of one molecule of water, transforms the one formula into the other. For the sake of clearness, the hydrogen and hydroxyl groups supposed to be removed during dehydration are printed on one side of the main chain of the carbohydrate :



Carbohydrate. Polyketide.

Up to the present this transformation has not been accomplished in the laboratory, since dehydrating agents carbonize the sugars so readily ; but it is obvious that the polyketides and the carbohydrates bear close structural relationships to one another, and a transformation of this sort is not beyond the powers of plant chemistry, which proceeds readily within a limited temperature range.

Another group of compounds remains for consideration. If, for the sake of simplicity, it be assumed that a molecule of methane is added to the polyketen chain instead of a molecule of water, as in the case given above, then a series of ketones can be derived from the polyketen structure. In this way, the relationship can be traced between the following polyketide derivatives :

$H.(CH_2.CO).CH_3$	=	Acetone	$CH_3.CO.CH_3$
$H.(CH_2.CO)_2.CH_3$	=	Acetylacetone	$CH_3.CO.CH_2.CO.CH_3$
$H.(CH_2.CO)_3.CH_3$	=	Diacetylacetone	$CH_3.CO.CH_2.CO.CH_2.CO.CH_3$

Thus, on purely theoretical grounds, it is possible to trace a

[1] Compare Collie, *J.*, 1907, **91**, 1806.

relationship linking together the carbohydrates, the polyketides, and these mono-, di-, and tri-ketones. In practice, as will be seen shortly, the ketones can be produced from the polyketides by quite simple reactions.

3. *Dehydracetic Acid*

Dehydracetic acid, $C_8H_8O_4$, was originally detected by Geuther[1] during his investigations on acetoacetic ester. In later times it has been obtained in a variety of ways, none of which throws a clear light upon its constitution. For example, it can be prepared by passing acetoacetic ester through a heated tube.[2] It is also produced by the direct polymerization of pure diketen,[3] by the action of tertiary bases upon acetyl chloride,[4] and, in small yield, by the action of phosphorus pentoxide upon acetic anhydride.[5] Acetone-dicarboxylic acid, on treatment with acetic anhydride and subsequent heating, yields dehydracetic acid.[6] It can also be prepared by acting on triacetic lactone with acetic anhydride in presence of sulphuric anhydride; though it is noteworthy that no dehydracetic acid is formed by the action of acetyl chloride upon triacetic lactone.

Dehydracetic acid is a white crystalline compound melting at 109° C. and boiling at 270° C. It gives a one per cent. solution in water, which is acid to litmus and shows an orange tint with ferric chloride. It forms a series of salts[7] having the general formula $C_8H_9O_5M$, where M is a monovalent metallic atom: and on heating to 120° C. these salts lose water and then have the general formula $C_8H_7O_4M$. The conductivity[8] of dehydracetic acid is very small, which proves that it contains no carboxyl radicle.

It will be convenient at this point to deal with the constitution of dehydracetic acid, which presents a still unsolved problem.

[1] Geuther, *Zeitsch. f. Chemie*, 1866 (2), **2**, 8.
[2] Oppenheim and Precht, *Ber.*, 1876, **9**, 323.
[3] Chick and Wilsmore, *J.*, 1910, **97**, 1978.
[4] Wedekind, *Annalen*, 1902, **323**, 246, 257; Staudinger, *Ber.*, 1905, **38**, 1735; Staudinger and Klever, *Ber.*, 1906, **39**, 968; Wedekind and Weisswange, *ibid.*, 1631.
[5] Diels and Meyerheim, *Ber.*, 1907, **50**, 362.
[6] Pechmann, *Ber.*, 1891, **24**, 3600.
[7] Collie and Le Sueur, *J.*, 1894, **56**, 254.
[8] Collie, *J*, 1900, **77**, 971.

Obviously dehydracetic acid is a structure derivable from two molecules of acetoacetic ester by the withdrawal of two molecules of alcohol :

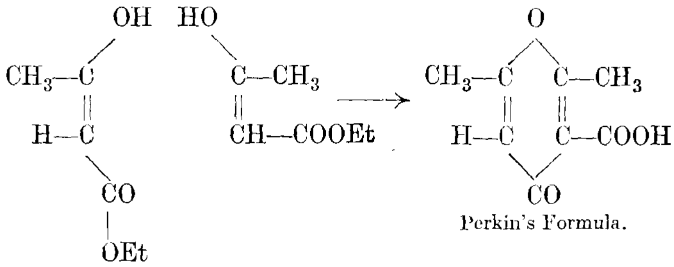
$$\underset{\text{Acetoacetic ester.}}{2C_6H_{10}O_3} - 2C_2H_5OH = \underset{\text{Dehydracetic acid.}}{C_8H_8O_4}$$

Now there are five possible ways in which this process can be assumed to take place, excluding unlikely methods. These five are shown on p. 109.

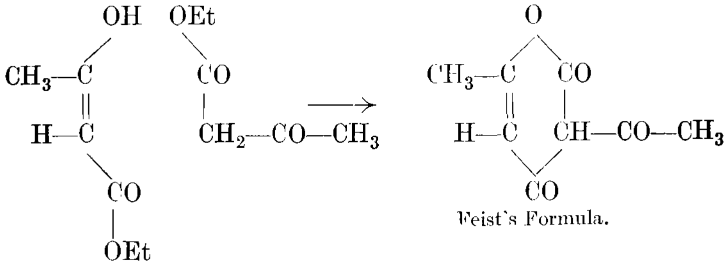
If both molecules of acetoacetic ester react in the enolic form, a compound having Perkin's formula is obtained. If one molecule reacts in the enolic and the other molecule in the ketonic form, we get a structure corresponding to Feist's formula.

The next set of formulæ are best understood by assuming that the condensation takes place in two stages, the first of which is the formation of a tetracetic ester chain, as shown in (III.), by the elimination of a molecule of alcohol between —COOEt of one molecule and the —CH_3 of the other.

This long chain may now lose another alcohol molecule in one of three ways. If an enolic hydroxyl group forms at the carbon atom (4), and alcohol is removed between this and the —OEt group at the end of the chain, Collie's formula is produced. If, instead, the alcohol molecule is derived from the hydrogen atom attached to the carbon atom marked (3) and the —OEt group at the end of the chain, then acetophloroglucinone is formed. Finally, if the alcohol molecule is derived from the ethoxy-group at one end of the chain and a hydrogen atom from the methyl radicle at the other extreme, a single tetraketo-octomethylene ring is obtained, which is shown in the last formula.



Perkin's Formula.

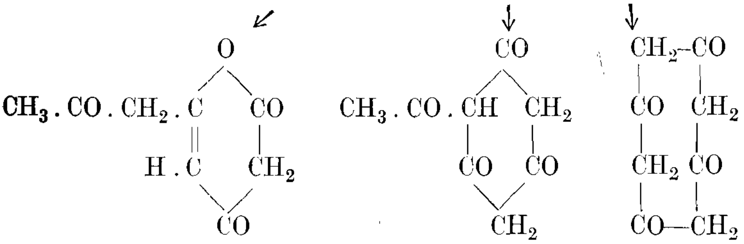


Feist's Formula.

$$CH_3 . CO . CH_2 . CO . OEt \quad + \quad CH_3 . CO . CH_2 . CO . OEt$$

$$\downarrow$$

$$\underset{1}{CH_3} . \underset{2}{CO} . \underset{3}{CH_2} . \underset{4}{CO} . \underset{5}{CH_2} . \underset{6}{CO} . \underset{7}{CH_2} . \underset{8}{COOEt} \quad + \quad EtOH$$



Collie's Formula. Acetophloroglucinone. Tetraketo-octomethylene.

We can now examine the relative probability of these five structures in the light of the properties of dehydracetic acid.

Perkin's formula is at once eliminated from consideration, since it contains a true carboxyl group. This would not agree with the low conductivity of dehydracetic acid.

The acetophloroglucinone formulæ also may be eliminated from the list of possible structures. This compound is known; and its properties [1] are different from those of dehydracetic acid.

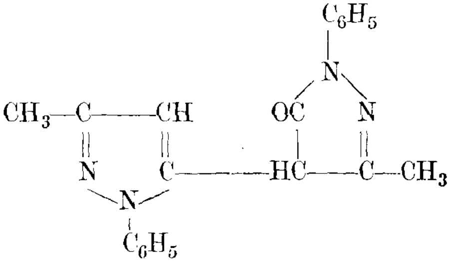
Feist's formula fails to account for the fact that when dehydracetic acid is treated with phosphorus pentachloride [2] it yields a substance $C_8H_6O_2Cl_2$. This reaction proves that dehydracetic acid has a structure which can develop two hydroxyl groups, probably by enolization. Inspection of the Feist formula will show that only one hydroxyl group can be formed, unless it be assumed that some carbon atom is left without any hydrogen

[1] Heller, *Ber.*, 1912, **45**, 418.

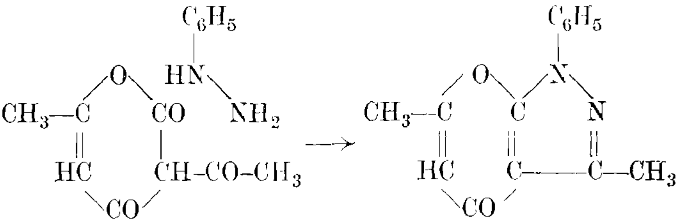
[2] Oppenheim and Precht, *Ber.*, 1876, **9**, 323.

and directly attached by double bonds to each of its neighbours, or that enolization takes place owing to a shift of a hydrogen from the methyl group in the side-chain, which is most improbable.

The Collie formula, while it meets this case perfectly, fails in another respect. Stollé studied the action of phenylhydrazine upon dehydracetic acid [1] and found that in addition to simple phenylhydrazone formation, a further loss of water occurred, leading to the synthesis of a pyrazol derivative and also to the formation, as a by-product, of phenyl-methyl-pyrazyl-phenyl-methyl-pyrazolene :

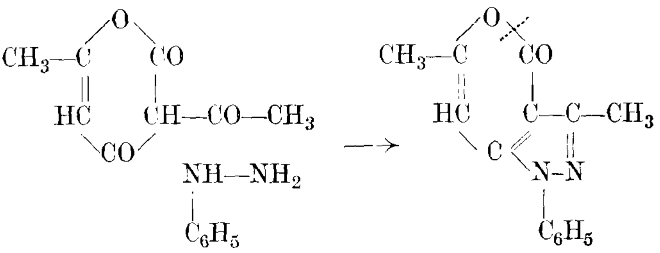


The Feist formula agrees with this work of Stollé, as the following will show. The reaction with phenylhydrazine can be expressed thus :


(I.)

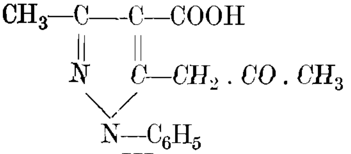
Feist's Formula.

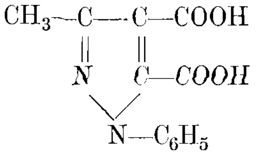
or,


(II.)

[1] Stollé, *Ber.*, **1905, 38,** 3026.

The choice between these two formulæ is easily made.[1] The compound, whether it be (I.) or (II.), when boiled with alcoholic potash, opens up into a substance $C_{14}H_{14}O_3N_2$, which contains an esterifiable carboxyl group, and a ketonic group capable of oximation. If formula (II.) were opened up by the addition of water at the dotted line, the compound (III.) would be obtained, which fulfils these requirements. Formula (I.), on the other hand, cannot be split open in any way which will yield the required result. The final proof is furnished by the fact that on oxidation, compound (III.) furnishes the known substance 1-phenyl-3-methyl-pyrazol-4, 5-dicarboxylic acid (IV).


(III.)


(IV.)

Inspection of formula (I.) will show that its production depends on the presence, in the dehydracetic acid molecule, of three carbonyl groups attached to a single carbon atom; and the same holds good for the formation of the pyrazyl-pyrazolone derivative formulated above. Since no such triple grouping of carbonyl radicles is to be found in the Collie formula, this suggested structure for dehydracetic acid does not agree with the facts.

The same objection invalidates the tetraketo-octomethylene formula mentioned above.

This leaves only Feist's formula intact; and even it is unable to account for the peculiar action of phosphorus pentachloride which has already been mentioned.

From the foregoing reasoning, it will be clear that even after half a century's work, we have not succeeded in producing a formula for dehydracetic acid which will fully express the character of the compound. As will be seen when the properties of dehydracetic acid are examined, the substance is extremely labile; and it seems possible that some of the anomalies can be explained by assuming intramolecular change to occur under the influence of the reagents employed.

With concentrated aqueous ammonia, dehydracetic acid reacts at ordinary temperatures, yielding a compound,

[1] Benary, *Ber.*, 1910, **43**, 1070.

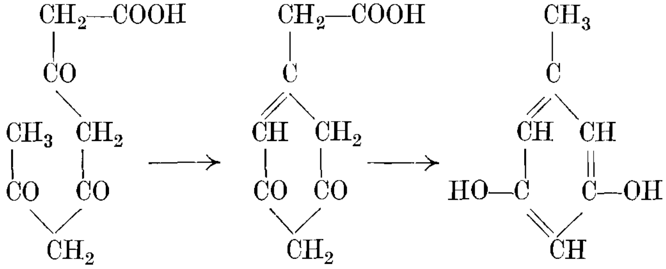
$C_8H_7O_3 . NH_2$, which loses ammonia and produces sodium dehydracetate when it is treated with caustic soda.*

On treatment with alkali, dehydracetic acid yields various results according to the conditions of the experiment. The simplest reaction is a hydrolysis of the type shown in the following equation :[1]

$$C_8H_8O_4 + 3H_2O = CO_2 + 2CH_3 . COOH + CH_3 . CO . CH_3$$

Malonic acid has also been detected among the decomposition products.[2] These results can easily be derived from Collie's formula ; but Feist's formula fails to account for the appearance of malonic acid.

A more complex change under the action of alkali has been observed by Collie.[3] The first stage is apparently an opening up of the dehydracetic acid ring, yielding the chain of tetracetic acid. This acid (I.) then loses a molecule of water as shown below, producing dihydroxy-phenylacetic acid (II.) which, by expelling carbon dioxide is converted into orcinol (III.) :



(I.) Collie's Formula. (II.) (III.)

This reaction can be expressed by means of the Collie formula, but it can also be made to agree with Feist's formula for dehydracetic acid.

Turning to the action of acids upon dehydracetic acid, the same sensitiveness to the conditions of experiment can be noted. When dehydracetic acid is heated to 135° C. for a short time with 90 per cent. sulphuric acid,[4] it is converted into triacetic lactone :

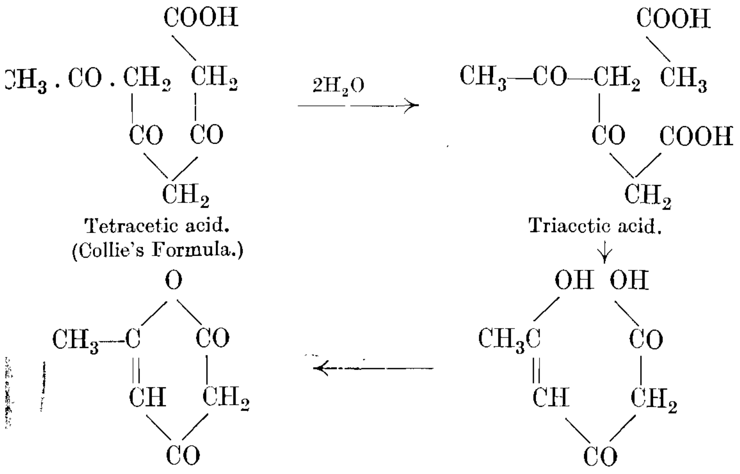
* Curiously enough, this forms an exact parallel to the behaviour of phloroglucinol, which with ammonia forms 1-amino-3, 5-dihydroxy-benzene (Pollak, *Monatsh.*, 1893, **14**, 401). This behaviour might be used to suggest a resemblance between dehydracetic acid and the benzene series.

1 Oppenheim and Precht, *Ber.*, 1876, **9**, 323.

2 Shibbye, *Dissertation*, Wurtzburg (1882), p. 5.

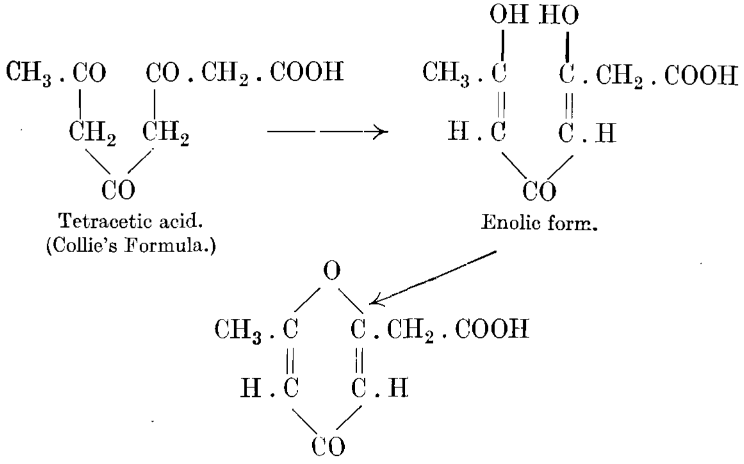
3 Collie, *P.*, 1907, **23**, 230.

4 Collie, *J.*, 1891, **59**, 607.



Tetracetic acid. (Collie's Formula.) Triacetic acid. Triacetic lactone.

This production of triacetic lactone, however, is not the only reaction brought about by the action of sulphuric acid. If we dilute the sulphuric acid a little, using eighty-five per cent. instead of ninety per cent. strength, the action takes quite a different course.[1] As in the previous case, water is added on, the ring opens and a tetracetic acid is formed; but, instead of breaking down into triacetic and acetic acids, the substance enolizes in a fresh place and again loses water to form a new acid:

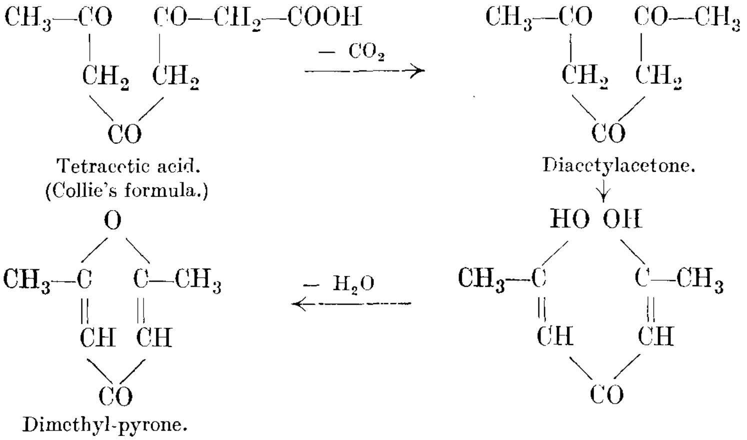


Tetracetic acid. (Collie's Formula.) Enolic form. Isomer of dehydracetic acid.

[1] Collie and Hilditch, *J.*, 1907, **91**, 787.

This sensitiveness to very slight variations in the reagents used is typical of the polyketide series, as will be seen later in the action of weak and stronger alkalis upon diacetylacetone.

The action of concentrated hydrochloric acid, again, differs from those of the two sulphuric acid solutions which have just been described. Boiling concentrated hydrochloric acid converts dehydracetic acid into dimethyl-pyrone. The reaction probably begins with the opening out of dehydracetic acid into the tetracetic acid chain, which then loses carbon dioxide and forms diacetylacetone. Enolization of the triketone leads to elimination of water and the production of the pyrone ring as shown below:

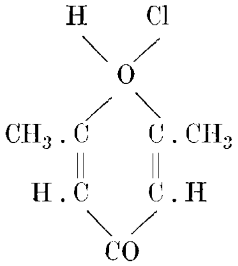


4. *Dimethyl-pyrone*

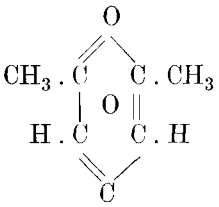
When the compound obtained by heating dehydracetic acid with hydrochloric acid is analyzed, it is found to have the composition $C_7H_9O_2Cl$, which corresponds to a compound of one molecule of dimethyl-pyrone with one molecule of hydrochloric acid. The substance is not a chlorine substituted pyrone derivative, but behaves exactly like the hydrochloride of an organic base. Collie and Tickle,[1] who were the discoverers of this class of substances, prepared a series of compounds of dimethyl-pyrone with many of the common acids, both organic and inorganic, as well as platinum double salts; and from a study of their properties they drew the conclusion that the

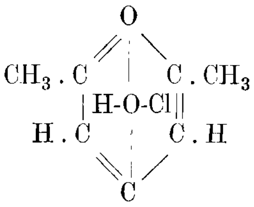
[1] Collie and Tickle, *J.*, 1899, **75**, 710.

oxygen atom which forms the bridge in the pyrone nucleus has basic properties akin to those of a tertiary nitrogen atom. Thus, just as tertiary amines form ammonium salts, divalent oxygen compounds may unite with acids to form *oxonium salts.* The compound of dimethyl-pyrone with hydrochloric acid would on this hypothesis be represented by the formula :



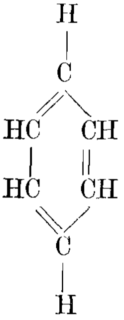
Dimethyl-pyrone is a white crystalline solid, subliming at low temperatures and easily soluble in most organic liquids. With acids it forms well-crystallized salts, soluble in, but hydrolyzed by water. Though it contains a carbonyl group, it does not react with either hydroxylamine or phenylhydrazine. This peculiar behaviour led Collie [1] to put forward the view that not one but both the oxygen atoms in the pyrone nucleus are quadrivalent in the oxonium salts ; while in the base itself one oxygen atom is supposed to be always quadrivalent. On this view the formulæ of dimethyl-pyrone and its hydrochloride would be written thus :

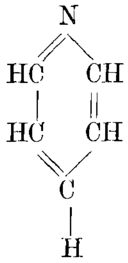


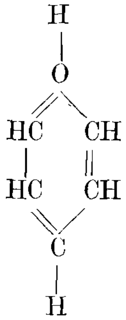


In both the above formulæ, the resemblance to the benzenoid type is manifest ; and Collie [1] was led to suggest that the root-substance of this class has a structure analogous to that of pyridine :

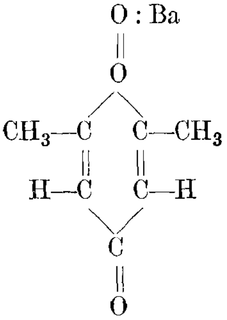
[1] Collie, *J.*, 1904, **85**, 971 ; cf. Willstätter and Pummerer, *Ber.*, 1905, **38**, 1461.

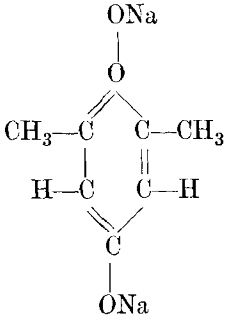

Benzene.

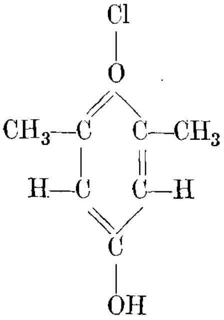

Pyridine.


Oxene.

Now by analogy with the oxene formula, the barium salt of dimethyl-pyrone should have the structure shown in (I.), the di-sodium salt should have the constitution (II.), and the hydrochloride of dimethyl-pyrone should be expressed by (III.).


Barium salt.


Di-sodium salt.


Hydrochloride.

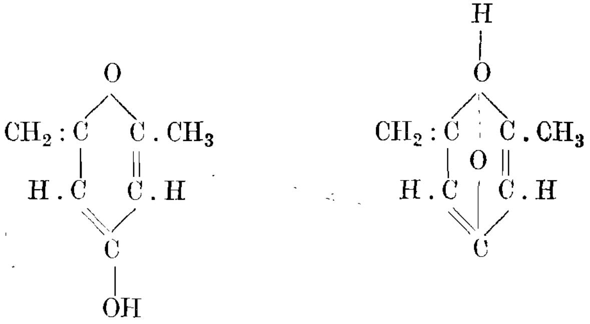
On this basis, the barium salt has a quinonoid structure, whilst the di-sodium salt and the hydrochloride are analogues of benzene. This agrees with the fact that the barium salt is canary-yellow in tint, whereas the di-sodium salt and the hydrochloride are colourless compounds.

This speculation of Collie's soon received confirmation by the discovery of the so-called benzo-pyroxonium or pheno-pyrylium salts [1] which are closely allied to the structures found in flower pigments.

This apparent analogy between the pyrone and benzene structures finds support in the existence of a substance,[2] pseudo-

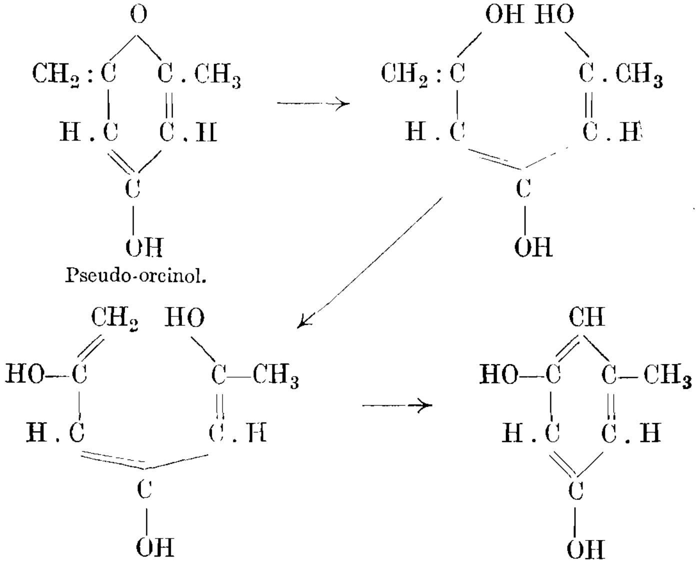
[1] Decker and Fellenberg, *Annalen*, 1907, **356**, 281 ; 1909, **364**, 17.
[2] Collie and Stewart, unpublished observations.

rcinol, which stands midway between the pyrone and benzene eries. On treatment with dilute alkali, dimethyl-pyrone is onverted into an isomer to which one or other of the following onstitutions may be ascribed :



Pseudo-orcinol.

)n boiling with acids, this substance is converted into the orresponding salt of dimethyl-pyrone, a change which obviously nvolves only the wandering of a hydrogen atom from oxygen to he methylene group. On treatment with strong alkali, this seudo-orcinol undergoes a more complicated reaction and ields orcinol :



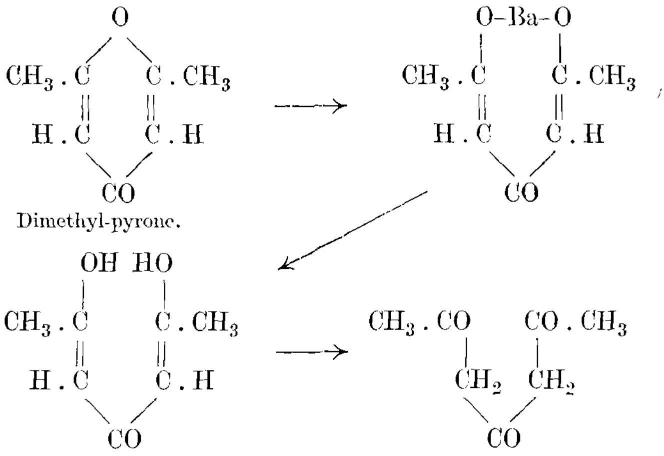
Pseudo-orcinol.

Orcinol.

Collie[1] obtained the corresponding diacetyl-derivative, which behaves similarly ; by acids it is converted into salts of diacetyl-dimethyl-pyrone, whilst alkalis change it into diacetyl-orcinol.

5. *Diacetylacetone*

We now come to one of the most protean of the polyketide derivatives, the triketone diacetylacetone. When dimethyl-pyrone is boiled with a strong solution of barium hydroxide, it yields a barium salt * which, on treatment with acids, liberates diacetylacetone : †



Dimethyl-pyrone.

Diacetylacetone.

Diacetylacetone is a colourless crystalline compound, easily volatile at ordinary temperatures. For some reason,[2] its central carbonyl group does not react with hydroxylamine, though the other two carbonyl radicles behave normally. It is sensitive to hydrolysis, breaking up into acetic acid and acetone.

Its most interesting reactions, however, are those in which dehydration takes place. Even at ordinary temperatures it is liable to a spontaneous loss of water, with the production of

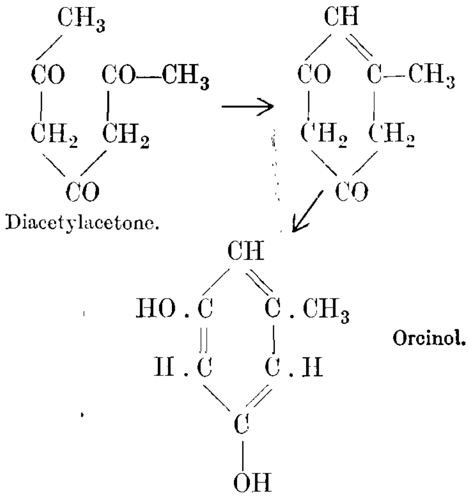
[1] Collie, *J.*, 1904, **85**, 971.

* The older formula of the barium salt is used here for the sake of simplifying the scheme. Compare p. 116.

† The details of the best method of preparation are given by Collie and Reilly, *J.*, 1922, **121**, 1984.

[2] See Collie, *J.*, 1904, **85**, 973.

dimethyl-pyrone. When acid dehydrating agents are used,[1] orcinol is formed:

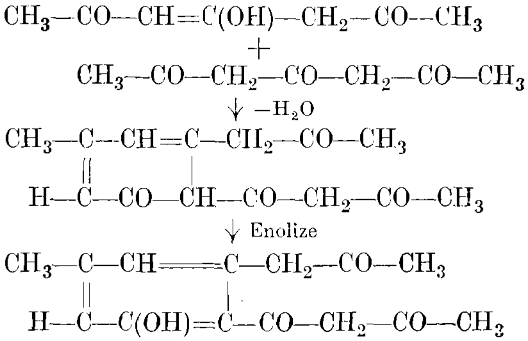


Diacetylacetone.

Orcinol.

Stronger dehydrating agents produce brilliant scarlet pigments [2] of unknown constitution, which can also be obtained by analogous methods from dimethyl-pyrone.

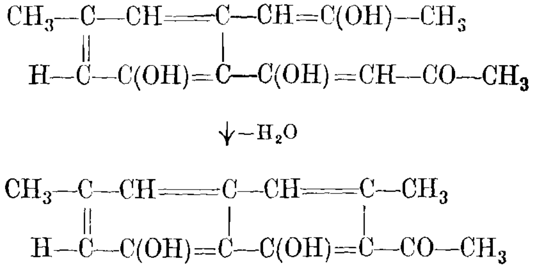
In alkaline solutions, diacetylacetone suffers dehydration also, and here too the mechanism of the reaction varies with the strength of the solution. In strongly basic solutions, orcinol is formed in the same manner, as is shown in the formulæ which have just been considered. If the alkali be very dilute, however, the end-product of the reaction is a benzene derivative, which is formed as follows from two molecules of diacetylacetone:



Benzene derivative.

[1] Collie and Myers, *J.*, 1893, **63**, 122. [2] Stewart, unpublished observation.

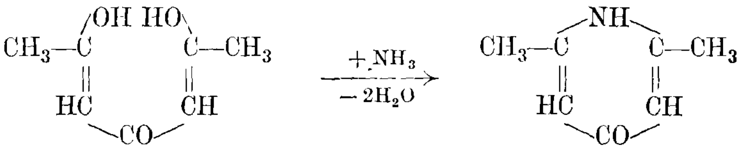
This new benzenoid compound in turn, under the action of slightly stronger alkali solutions, loses a molecule of water and yields a naphthalene derivative:



Naphthalene derivative.

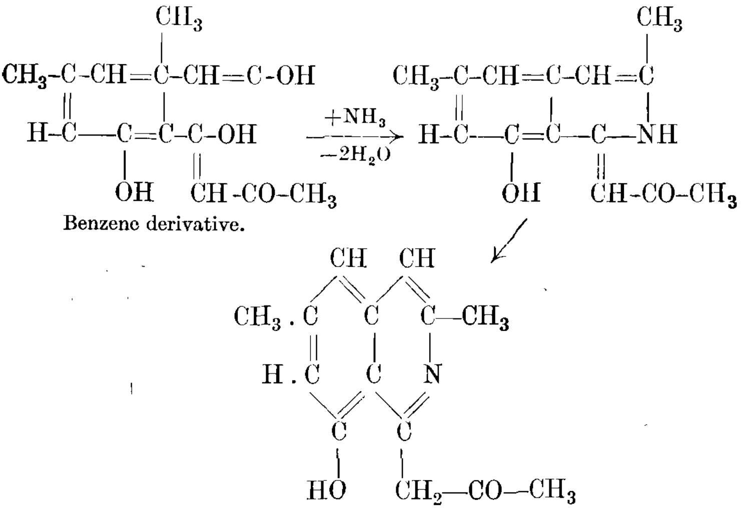
Hitherto the compounds described have contained only carbon, hydrogen, and oxygen; but at this point it may be well to show that cyclic nitrogen derivatives can also be obtained from diacetylacetone by simple dehydration reactions involving ammonia.

In presence of ammonia, diacetylacetone reacts in the di-enolic form, losing two molecules of water and introducing the —NH— radicle to form lutidone, a pyridine derivative:



Diacetylacetone. Lutidone.

Similarly, ammonia reacts with the benzene derivative described above to yield an isoquinoline compound:



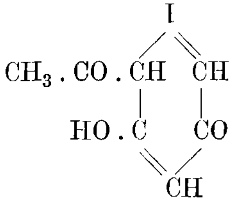
Benzene derivative.

Isoquinoline derivative.

Among the other properties of diacetylacetone, the following may be mentioned.[1] Methyl sulphate and phosphorus pentachloride merely dehydrates it to form dimethyl-pyrone. Zinc ethyl, formaldehyde and benzaldehyde do not attack it. Phenylhydrazine forms a compound $C_{19}H_{20}N_4$; semicarbazide yields a semicarbazone; hydroxylamine reacts, but the product is a deliquescent liquid which decomposes on heating and has not been induced to crystallize. With urea, diacetylacetone forms a crystalline material which apparently has the formula $C_8H_9O_3N$.

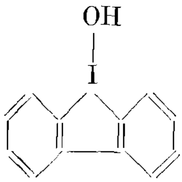
It is worth noting that the peculiarities of diacetylacetone are paralleled by certain abnormalities observed in acetylacetone.[2]

When iodine acts on the barium salt of diacetylacetone [3] a peculiar substance is produced with properties which are best expressed by the formula:



[1] Collie and Reilly, *J.*, 1922, **121**, 1984.
[2] Morgan andDrew, *J.*, 1922, **121**, 928.
[3] Collie and Reilly, *J.*, 1921, **119**, 1550

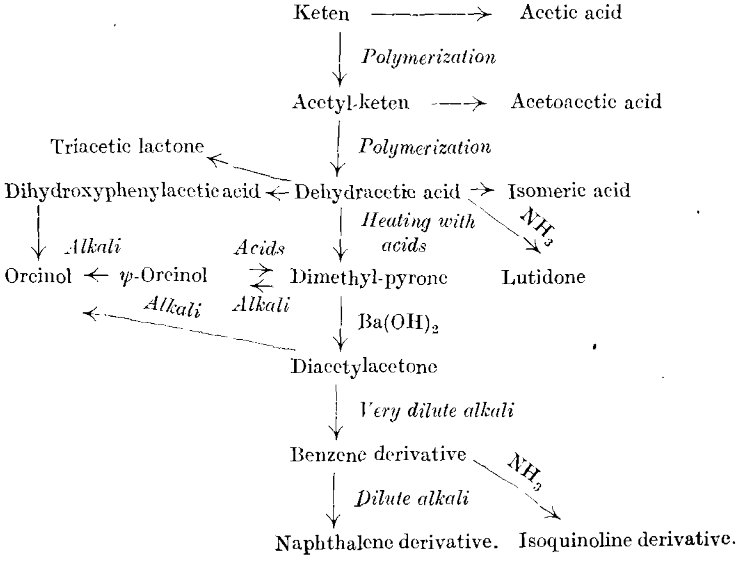
On solution in water, the iodine atom becomes quinquevalent; and a strong acid is formed, which seems to be due to the addition of H and OH to the iodine atom. This distinguishes the compound from the hydroxy-derivatives of trivalent iodine such as diphenyl-iodonium hydroxide: $(C_6H_5)_2I \cdot OH$, which is a strong base, and even from the other known case [1] in which iodine acts as a hetero-ring member,



since this also is a basic substance.

6. *Conclusion*

In the foregoing parts of this chapter a number of relationships have come to light between various substances, and perhaps it may be well at this point to insert a tabular scheme showing these relationships in a more compact form:



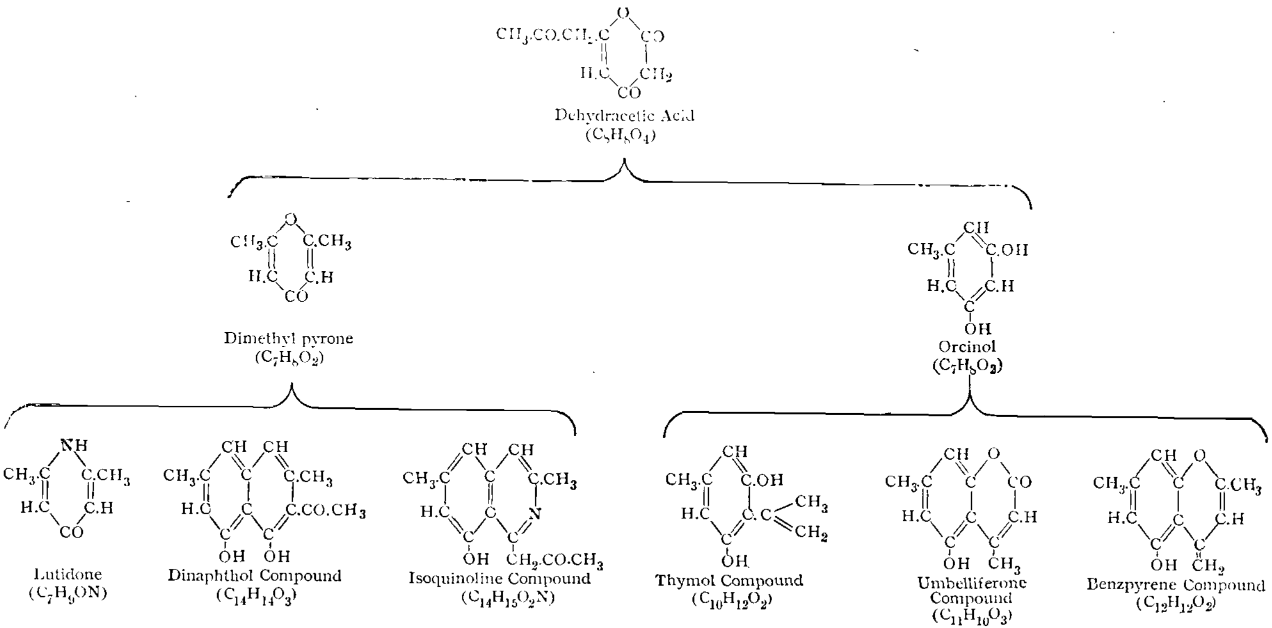
[1] Mascarelli, *Atti R. Accad. Lincei*, 1908 (v), 17, ii. 580; *Gazetta*, 1908, **38**, ii. 619.

In addition to the compounds shown here, three others may be mentioned in passing. From dimethyl-pyrone and acetoacetic ester, Collie has obtained an umbelliferone derivative, which on hydrolysis loses carbon dioxide and yields a derivative of the thymol type. Again, by condensing acetylacetone with dimethyl-pyrone, a benzpyrene compound is obtained. The structures of these substances are shown in the table on p. 124, which also brings to light the genetic relationships between the more interesting derivatives of the polyketide series.

Examination of these two tables will reveal at once the position of the polyketide group as key-substances in organic chemistry. In the aliphatic series they give rise to acids, ketones, ketonic acids, and diketones. In the aromatic group their derivatives include compounds of benzene and naphthalene as well as representatives of the phenols. Among the heterocyclic substances, the polyketide derivatives yield members of the pyrone, benzopyrone, benzpyrene, pyridine, and isoquinoline series.

What is specially noteworthy is the fact that all these varied compounds are derived from the parent polyketide derivatives by the three simplest reactions of organic chemistry : the addition of water, the removal of water, and the loss of carbon dioxide. Here, evidently, is one of the closest analogies to the chemistry of the plants themselves ; and it is of no little interest to observe that the polyketide products contain classes which are also found widely distributed through the vegetable world, such as the pyrones, the isoquinoline group, orcinol, etc.

If we consider together the ketens and the polyketides, some simple general principles make themselves obvious at once. Keten and diketen are remarkable for their great reactivity. They possess the power of polymerization to a marked degree. Their union with acid or neutral substances produces compounds which in turn are reactive, though not to the same extent as the parent bodies ; but if, on the other hand, the ketens be combined with basic substances, the products are not at all reactive. The higher members of the polyketen group when combined with water tend spontaneously to lose carbon dioxide, and become converted into ketonic compounds of a lower series, which in turn may be dehydrated to form comparatively stable benzenoid or pyrone derivatives. Thus these substances as a class illustrate



Dehydracetic acid . $\begin{cases} C_8H_8O_4 - CO_2 \rightarrow C_7H_8O_2 \text{ . . . . Dimethyl-pyrone.} \\ C_8H_8O_4 - CO_2 \rightarrow C_7H_8O_2 \text{ . . . . Orcinol.} \end{cases}$

Dimethyl pyrone . $\begin{cases} C_7H_8O_2\text{—isomeric change} \rightarrow C_7H_8O_2 \text{ . . . . Orcinol.} \\ C_7H_8O_2 + NH_3 - H_2O \rightarrow C_7H_9ON \text{ . . . . Lutidone.} \\ 2C_7H_8O_2 + 2H_2O - 3H_2O \rightarrow C_{14}H_{14}O_3 \text{ . . . . Naphthalene Compound.} \\ 2C_7H_8O_2 + 2H_2O + NH_3 - 4H_2O \rightarrow C_{14}H_{15}O_2N \text{ . . . . Isoquinoline Compound.} \end{cases}$

$C_7H_8O_2 + H(CH_2CO)_2OH - 2H_2O \rightarrow C_{11}H_{10}O_3$ . . . Umbelliferone Compound.
$C_{11}H_{10}O_3 + H_2O - CO_2 \rightarrow C_{10}H_{12}O_2$ . . . Thymol Compound.
$C_7H_8O_2 + C_5H_8O_2 - 2H_2O \rightarrow C_{12}H_{12}O_2$ . . . Benzpyrene Compound.
(Acetylacetone)

the dual tendencies at work in the whole field of organic chemistry —the synthetic and the analytic; the simpler, more reactive group tending always to attract other atoms and form more complex derivatives, while these in turn become unstable and break down into new and more stable forms.

CHAPTER VII

THE MONOCYCLIC TERPENES

1. *Introductory*

WHEN the saps and tissues of certain plants (such as pines, camphor, lemons, and thyme) are distilled, the distillates are found to contain among other things a mixture of substances which are classed under the general head of ethereal oils. For the most part these ethereal oils contain unsaturated hydrocarbons of the general formula $(C_5H_8)_n$ (or derivatives of these substances), and these may be divided into three classes—

1. Open-chain olefinic compounds.
2. Monocyclic hydrocarbons (reduced benzene derivatives).
3. Cyclic compounds containing more than one ring.

In the naturally occurring compounds it is found that by far the greater number of these hydrocarbons have the empirical formula $C_{10}H_{16}$; and it is not without interest that Collie,[1] in polymerizing ethylene by means of the silent electric discharge, found that the major part of the substance used was converted into compounds containing either ten or fifteen carbon atoms.

The nomenclature of these substances is at present somewhat in confusion. It has been customary to apply the name terpene to any compound having the composition C_5H_8, or any polymeric variety of this type. This general type was then divided into two others: the "true terpenes," cyclic substances of the formula $C_{10}H_{16}$; and the "olefinic terpenes," which are open-chain bodies having the formulæ C_5H_8 and $C_{10}H_{16}$. Another system of nomenclature classes the whole group under three heads: hemi-terpenes C_5H_8; terpenes, $C_{10}H_{16}$; and sesquiterpenes, $C_{15}H_{24}$. The naturally occurring mono-cyclic

[1] Collie, *J.*, 1905, **87**, 1540.

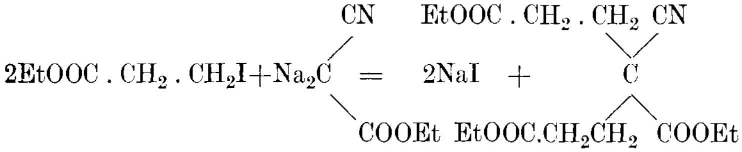
terpenes are for the most part derived from either *m*- or *p*-hexahydrocymene.

Most of the terpenes are colourless, pleasant-smelling liquids of high refractive power. They boil without decomposition, and are volatile in steam. Some are optically active, some inactive by racemization, while others, containing no asymmetric carbon atom, cannot show activity at all.

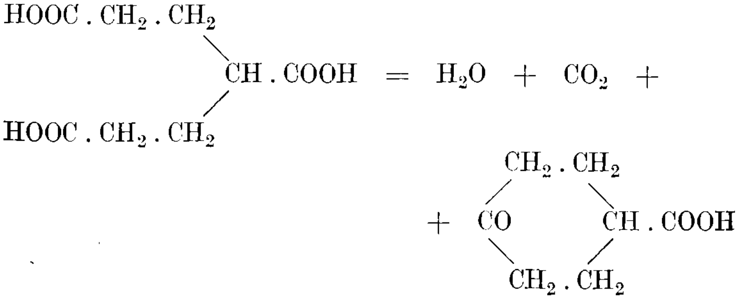
2. *The Synthesis of Terpineol*

In the group of the monocyclic terpenes, by far the most important compound is terpineol, for from it most of the other members of the group can be prepared, either directly or indirectly. The constitution of terpineol, therefore, is of considerable value in determining the constitutions of other substances. The inactive form of terpineol has been synthesized by Perkin,[1] and as this synthesis establishes the constitution of the substance, it will be described here step by step.

When β-iodo-propionic ester was allowed to interact with the disodium derivative of cyan-acetic ester, γ-cyano-pentane-$\alpha\gamma\epsilon$-tricarboxylic ester was produced :

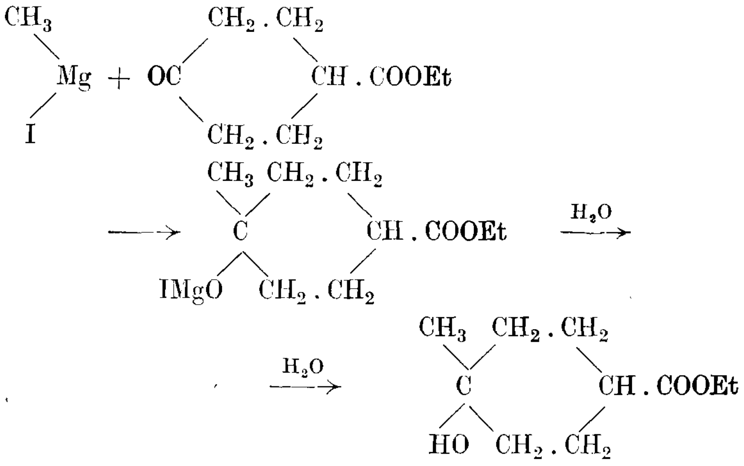


From this the free acid was obtained by hydrolysis with hydrochloric acid, and when it was boiled with acetic anhydride and then distilled, it was transformed by loss of water and carbon dioxide into δ-keto-hexahydrobenzoic acid :

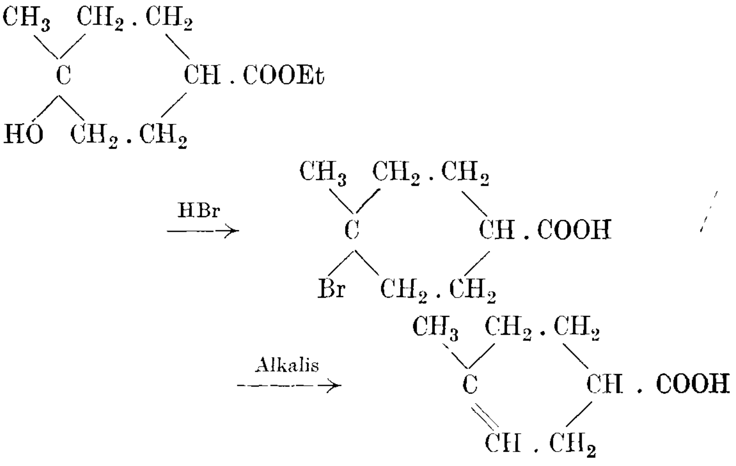


[1] Perkin, *J.*, 1904, **85**, 654.

Grignard's reaction was then applied to the ester of this acid, magnesium methyl iodide being allowed to react with the ketonic group, and in this way δ-hydroxy-hexahydrotoluic ester was formed :

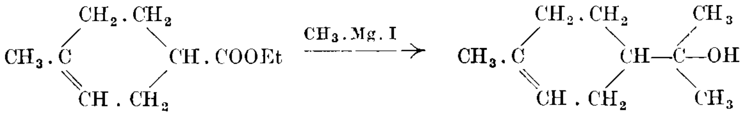


When, by the action of fuming hydrobromic acid, we replace the hydroxyl group in this acid by a bromine atom and then remove hydrobromic acid from the compound by means of weak alkalis or pyridine, we obtain Δ^3-tetrahydro-*p*-toluic acid :



After esterifying the acid, the Grignard reaction can be again employed, with the result that the ester group is attacked

and on treatment with water the intermediate compound breaks down into inactive terpineol.



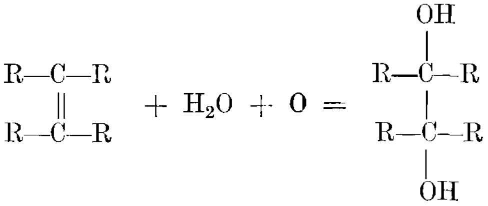
Terpineol.

If this synthesis be examined step by step it will be seen that there can be no doubt as to the constitution of terpineol, for the reactions can only be supposed to take place in the way shown. Any alternative formulation of any of the reactions would at once lead to contradiction in the later experiments.

An optically active terpineol has been prepared by Fisher and Perkin [1] by resolving the intermediate acid into dextro and lævo forms before continuing the synthesis.

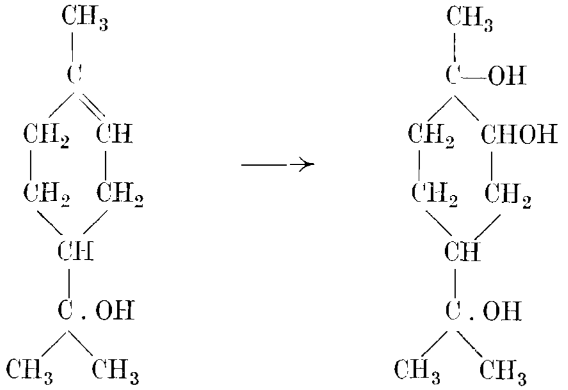
3. *The Decomposition Products of Terpineol*

It has been shown by Wagner [2] that when a compound containing a double bond is oxidized by means of potassium permanganate, the first step in the process is the breaking of the double bond and the addition of a hydroxyl group to each of the atoms between which the double bond originally lay—



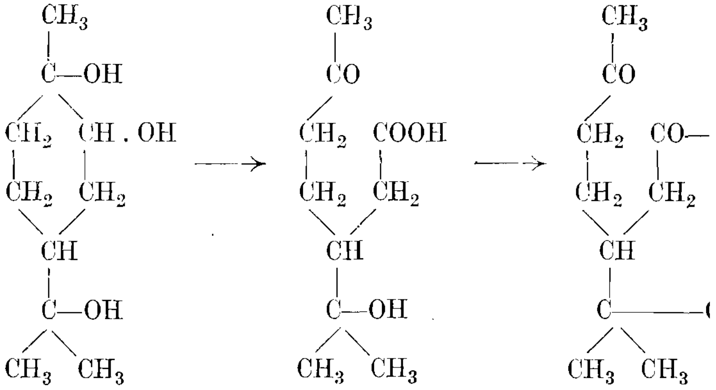
In the case of terpineol this rule holds, and it is found that the first oxidation product [3] obtained by the action of permanganate upon terpineol is trihydroxyhexahydrocymene—

[1] Fisher and Perkin, *J.*, 1908, **93**, 1871.
[2] Wagner, *Ber.*, 1888, **21**, 1230, 3359; 1891, **24**, 683.
[3] Wallach, *Annalen*, 1893, **275**, 150.



Terpineol. Trihydroxyhexahydrocymene.

This substance, on further oxidation,[1] is converted into homc terpenylic methyl ketone by the rupture of the single bon between the two hydroxyl-bearing carbon atoms—

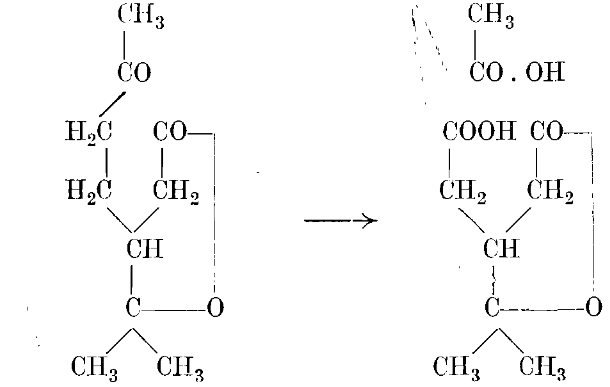


Trihydroxyhexa-hydrocymene. Intermediate acid. Homoterpenylic methyl ketone.

As is shown in the formulæ, the first product of the oxida tion is a hydroxy-acid which loses water at once between it carboxyl and hydroxyl groups, yielding the keto-lacton This keto-lactone is the first product which can be isolate when terpineol is oxidized with chromic acid, for the action i so violent that the trihydroxyhexahydrocymene is destroye as soon as it is formed.

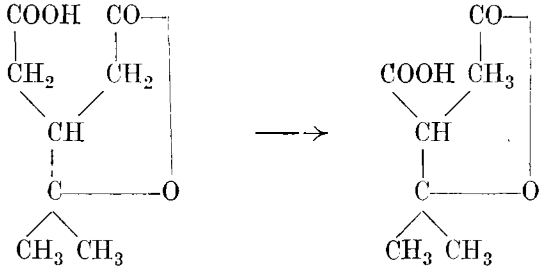
[1] Wallach, *Annalen*, 1893, **275**, 150; *Ber.*, 1895, **28**, 1773; Tiemann an Schmidt, *ibid.*, 1781.

Further oxidation with potassium permanganate[1] converts the keto-lactone into a mixture of acetic and terpenylic acids—



Homoterpenylic methyl ketone. Terpenylic acid.

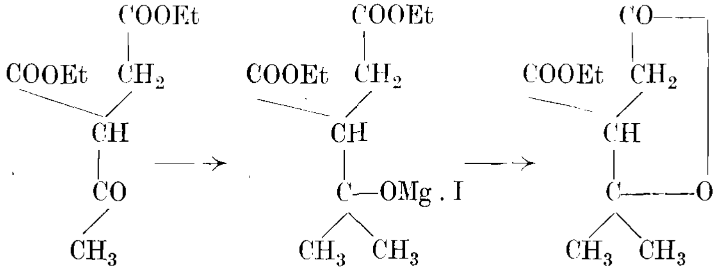
The latter substance, by the action of a 5 per cent. solution of permanganate, is still further decomposed into terebic acid—



Terpenylic acid. Terebic acid.

It will be seen that these formulæ for homoterpenylic, terpenylic, and terebic acid illustrate the decomposition of terpineol quite satisfactorily. Any doubt as to their accuracy was removed by the synthesis of the three acids, which was carried out by Simonsen.[2] Terebic[3] and terpenylic acid[4] had previously been synthesized in different ways. The Simonsen syntheses depend on the application of Grignard's reaction to various ketonic esters. From magnesium methyl iodide and acetyl-succinic ester he obtained terebic ester—

[1] Wallach, *Ber.*, 1895, **28**, 1776.
[2] Simonsen, *J.*, 1907, **91**, 184.
[3] Blaise, *C. R.*, 1898, **126**, 349.
[4] Lawrence, *J.*, 1899, **75**, 531.



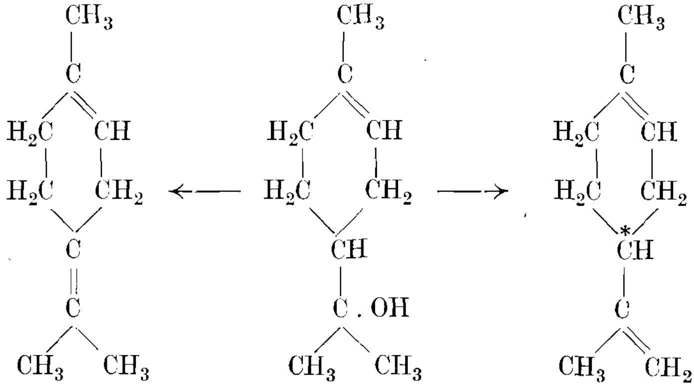
Acetyl-succinic ester. Terebic ester.

In exactly the same way β-acetyl-glutaric ester is converted into terpenylic ester, and β-acetyl-adipic ester into homo-terpenylic ester.

The constitution of terpineol, then, may be considered to be completely established, both synthesis and degradation products agreeing with the theory.

4. *The Constitution of Dipentene*

When terpineol is heated with acid potassium sulphate it loses a molecule of water, and is converted into dipentene. It is evident that this elimination of water may be represented in either of two ways :



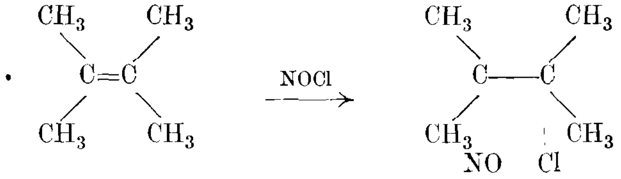
(I.) Terpineol. (II.)

Now, dipentene can be obtained by mixing together equal quantities of dextro- and lævo-limonene. It is, therefore, the racemic form of limonene, and must contain an asymmetric carbon atom. Formula (I.) contains no such carbon atom,

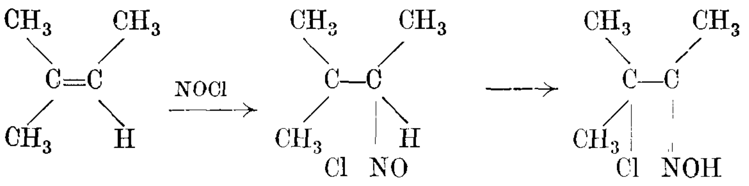
but the atom in (II.), which is marked with an asterisk, is asymmetric. Dipentene, then, must have the constitution represented by (II.).

In order to satisfy ourselves that this formula is the correct one, we may test it by seeing how far it agrees with some decompositions which dipentene can be made to undergo.

When nitrosyl chloride is allowed to act upon a compound containing a double bond it may unite with it in either of two ways.[1] If the double bond lies between two tertiary carbon atoms, the chlorine atom attaches itself to the one and the nitroso-group to the other, and the resulting substance is a *blue* nitroso-derivative:



On the other hand, if one of the carbon atoms is a tertiary and the other a secondary one, the chlorine of the nitrosyl chloride attaches itself to the tertiary atom and the nitroso-group to the secondary atom. The hydrogen atom then wanders, as shown in the formulæ below, with the result that a *colourless iso*-nitroso-compound is formed:

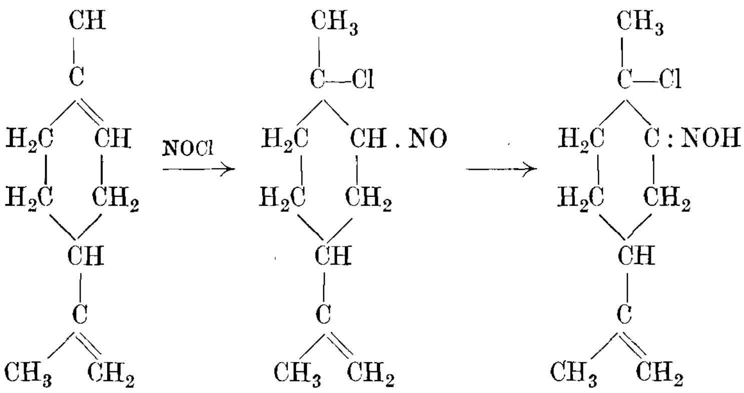


We must now turn to the case of dipentene; and to make reference easy we shall number each step.

I. When nitrosyl chloride acts upon dipentene, it might be supposed that it could react either with the double bond in the nucleus or with that in the side-chain. It actually attacks the nuclear double bond, as we shall show later, and to avoid the complication of two sets of formulæ we may confine ourselves to the case of the addition to the double bond of the

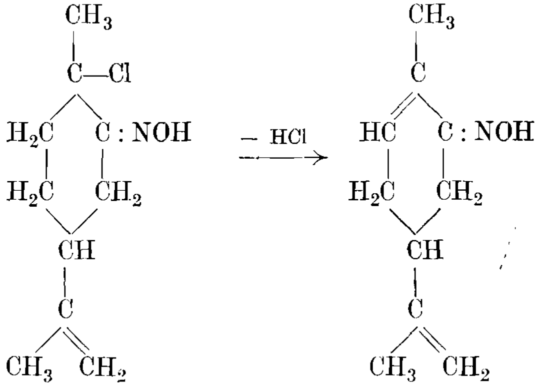
[1] Thiele, *Ber.*, 1894, **27**, 455.

nucleus. The reaction, if our formula for dipentene be correct, will take the course shown below :



Dipentene.

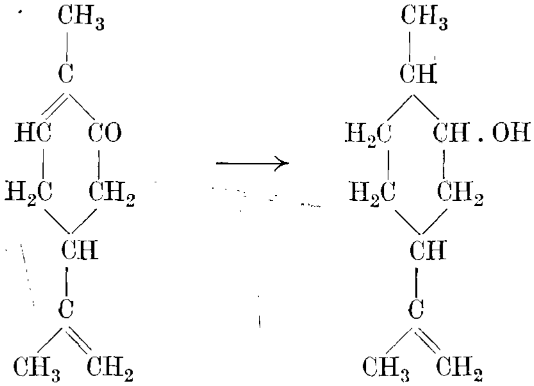
II. When the nitrosochloride formed in the last reaction is treated with alcoholic potash it loses one molecule of hydrochloric acid, and is transformed into a compound which proves to be identical with the oxime of the ketone carvone. This can be expressed as follows :—



Dipentene nitrosochloride. Carvoxime.

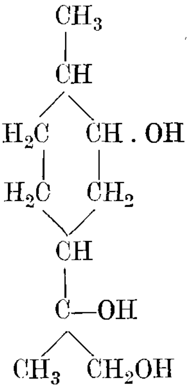
III. By hydrolysis of the oxime, carvone is produced.

IV. Carvone, on reduction, gives dihydrocarveol. This reduction might be supposed to take place either in the nucleus or in the side-chain. As will be shown later (VI.), the nucleus is reduced and the side-chain left untouched. We need not concern ourselves with the alternative set of formulæ, but may again confine ourselves to the one set :

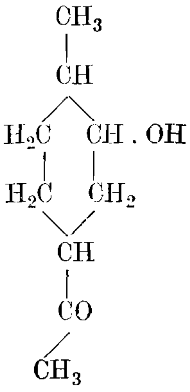


Carvone. Dihydrocarveol.

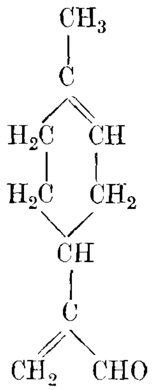
V. On oxidation, dihydrocarveol gives a trihydroxyhexahydrocymene—



VI. On further oxidation a ketone alcohol is formed:

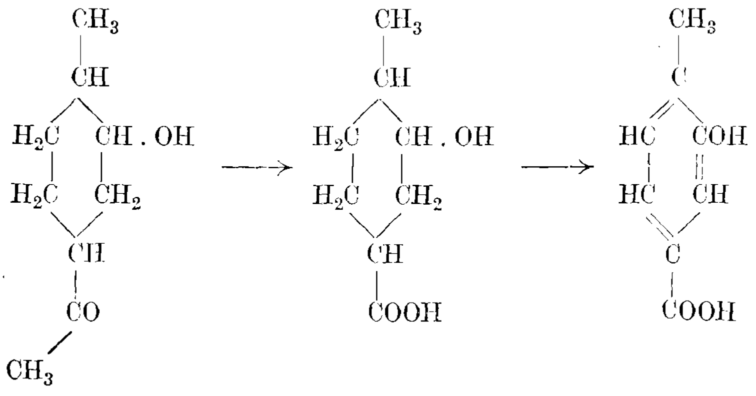


The production of this substance proves what was previously stated in I. and IV., *viz.*, that the nitrosyl chloride attacks the nucleus, and that in the reduction to dihydrocarveol the side-chain double bond is not reduced. If the nitrosyl chloride had attacked the side-chain we should, at Stage III., have formed an aldehyde of the type:



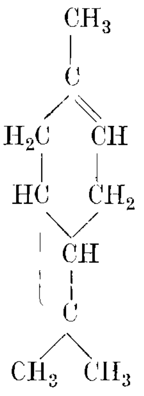
instead of the ketone produced in practice. If the side-chain had been reduced in Stage IV. instead of the nucleus, the nucleus would have been attacked by the oxidizing agent in Stage V., the ring would have been broken, and a ketonic *acid* would have been formed, just as in the case of the oxidation of terpineol.

VII. Further oxidation of the ketonic alcohol produced in Stage VI. yields a hydroxy-acid, which, by the action of bromine at 190° C., loses six hydrogen atoms, and is converted into hydroxy-*p*-toluic acid:

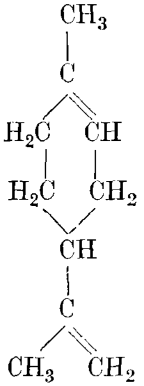


The results of this reasoning can be briefly summarized. The reactions IV. to VII. prove that the "isopropyl group" contains a double bond, which must also be present in dipentene. Moreover, since this double bond has persisted throughout the whole series of reactions I. to IV., it cannot have been the point at which the nitrosyl chloride attached itself, as this portion of the molecule has given rise to the —CH.OH— group. Further, the nitroso-group must have attached itself to the carbon atom to which the hydroxyl group is attached in the aromatic acid, *i.e.*, the one next that which carries the methyl group. These reactions can be explained only by assuming that dipentene has the structure which we attributed to it on account of its synthesis from terpineol.

It might be objected that we have not taken into account the possibility that, in the formation of dipentene, the elimination of water from terpineol may take place between two *non-adjacent* carbon atoms, giving rise to some such compound as :



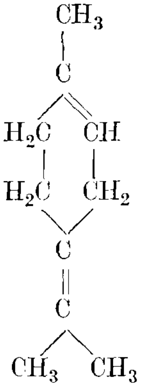
Any attempt to explain the question on these lines leads, however, to impossible results, and it may be taken as proved beyond doubt by the above experimental data that the structure of dipentene is as shown in the annexed formula. This, in turn, proves the formulæ of dextro- and lævo-limonene, for as they are the optical antipodes of which dipentene is the racemic variety, they also must possess the same structural formula as dipentene :



Dipentene.

5. *The Constitutions of Terpinolene and Terpinene*

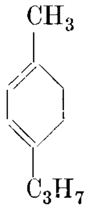
In the last section it was pointed out that the dehydration of terpineol might follow either of two courses: the one leading to a compound containing an asymmetric carbon atom, the other to a symmetrical derivative. The result of dehydration by means of acid potassium sulphate was shown to be dipentene; but when terpineol is dehydrated [1] by means of alcoholic sulphuric acid, an isomeric compound is formed which has the second of the two possible formulæ. This substance is terpinolene:



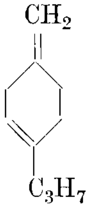
When terpinolene is treated with acids, it is converted into a substance which was originally assumed to be a single hydrocarbon, terpinene; and for a considerable time the constitution

[1] Wallach, *Ber.*, 1879, 12, 1022.

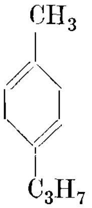
of terpinene was one of the riddles of organic chemistry. From the results of his investigations, Wallach [1] deduced that there is no such thing as a pure "terpinene"; but that the material to which this name has been given is a mixture of three different chemical individuals for which he proposed the following names and formulæ:—



α-Terpinene.



β-Terpinene.

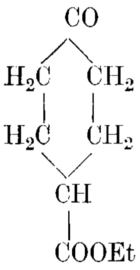


γ-Terpinene.

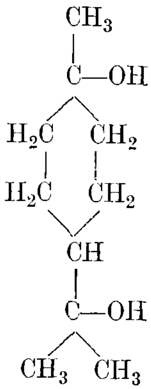
6. *Terpin and Cineol*

It will be recalled that both the carbonyl group and the —COOEt radicle yield tertiary alcoholic groups when treated with the Grignard reagent.

Kay and Perkin [2] have combined these two reactions into one by using a ketonic ester and allowing both vulnerable groups to be attacked simultaneously. By this means, from cyclohexanone-4-carboxylic ester, they obtained the dihydric alcohol, terpin:



Cyclohexanone-4-carboxylic ester.



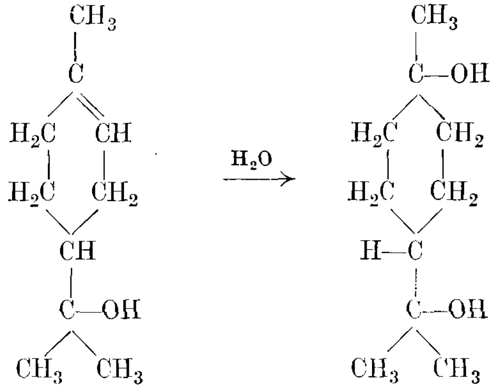
Terpin.

[1] Wallach, *Annalen*, 1910, **374**, 224; 1906, **350**, 142; *Terpene und Campher*, 1906, pp. 467–81.

[2] Kay and Perkin, *J.*, 1907, **91**, 372.

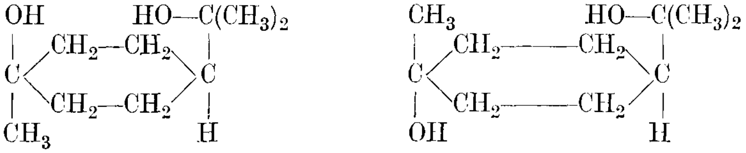
This synthesis proves the formula of terpin beyond any dispute.

Terpin may be also obtained by boiling terpineol with dilute sulphuric acid :



Terpineol. Cis-terpin.

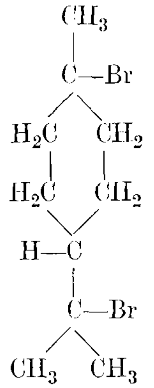
The terpin which is obtained in either of these ways is called *cis*-terpin, from the fact that in its space formula the two hydroxyl groups lie on the same side of the hexamethylene ring, while in the isomeric compound, *trans*-terpin, they lie on opposite sides of the ring :



Cis-terpin. Trans-terpin.

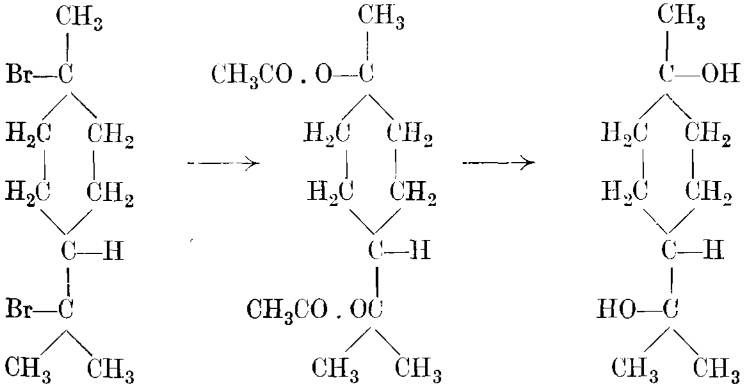
Cis-terpin unites with one molecule of water to form terpin hydrate, a crystalline substance from which it can be regenerated at 100° C. The trans-isomer does not unite with water at all.

Cis-terpin cannot be directly converted into trans-terpin, but the change can be effected by a somewhat roundabout method. In the first place, cis-terpin is subjected to the action of hydrobromic acid, by which means a dibromide is formed. As can be seen from its formula, this substance is identical with the hydrodromide of dipentene :



Dipentene dihydrobromide
(Cis-terpin dibromide).

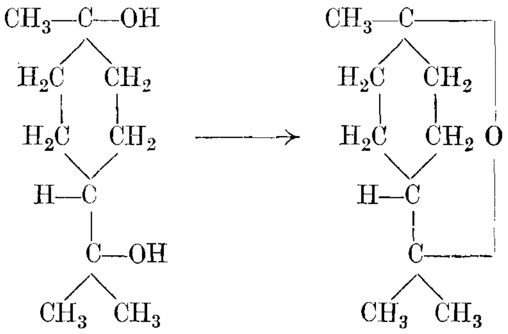
This dibromide is next treated with silver acetate in acetic acid solution, and the diacetate so produced is hydrolysed with alcoholic potash, yielding *trans*-terpin :



It should be noted that when cis-terpin is converted into its dibromide the product is the *cis*-form of dipentene dihydrobromide ; while, on the other hand, the action of hydrobromic acid on trans-terpin produces the *trans*-variety of dipentene dihydrobromide. Thus the change of cis-terpin into trans-terpin cannot be carried out through the bromides alone, as during their formation no change from cis- to trans-form takes place ; this only occurs during the hydrolysis of the acetyl derivative.

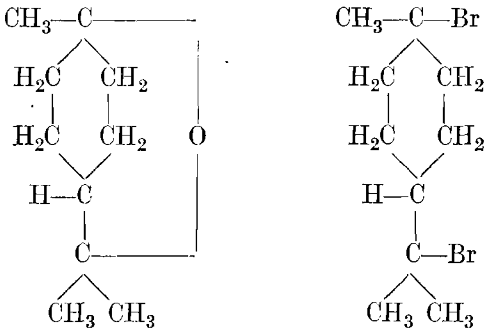
When cis-terpin is dehydrated, it yields a variety of products (terpineol, dipentene, terpinene, and terpinolene), among

which is found the compound cineol, $C_{10}H_{18}O$. This substance contains neither a hydroxyl nor a carbonyl radicle, and must therefore be an ether. On this view, its formation from cis-terpin is easily explained:



Cis-terpin. Cineol.

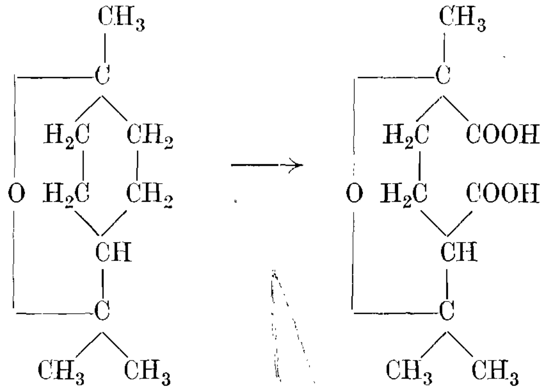
This formula is supported by the fact that hydrobromic acid in acetic acid solution converts cineol into cis-dipentene dibromide:



Cineol. Cis-terpin dibromide.

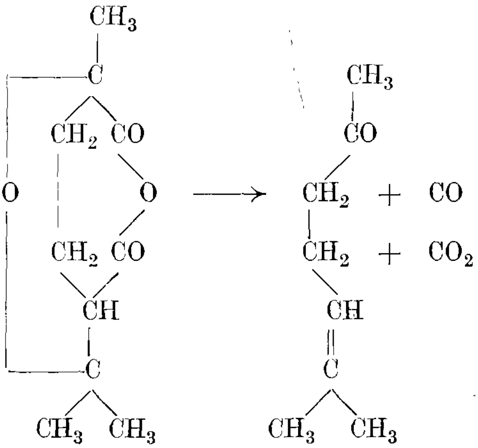
The behaviour of cineol on oxidation with potassium permanganate is curious.[1] The first effect is to break the hexamethylene ring, while leaving the ether chain untouched; in this way cineolic acid is produced:

[1] Wallach and Gildemeister, *Annalen*, 1888, **246**, 268; Wallach, *ibid.*, 1890, **258**, 319; Wallach and Elkeles, *ibid.*, 1892, **271**, 21.



Cineol. Cineolic acid.

When cineolic acid is treated with acetic anhydride it yields cineolic anhydride, which, on dry distillation, breaks down quantitatively into carbon monoxide, carbon dioxide, and methyl-heptenone, an aliphatic ketone of considerable interest from its relations to the terpenes—



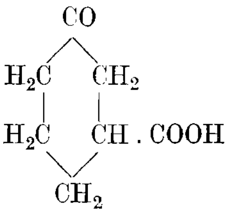
Cineolic anhydride. Methyl-heptenone.

7. *The Synthesis of Carvestrene*

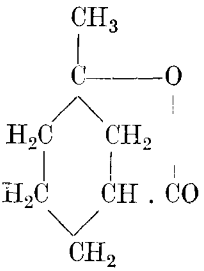
Perkin and Tattersall[1] have synthesized carvestrene by a series of reactions analogous to those employed by Perkin in

[1] Perkin and Tattersall, *J.*, 1907, **91**, 480.

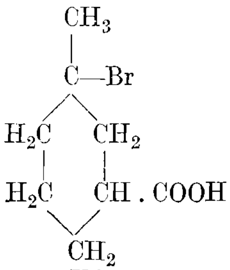
his synthesis of terpineol. The starting-point of this new synthesis was *m*-hydroxy-benzoic acid. This was first reduced with sodium and alcohol, forming hexahydro-*m*-hydroxy-benzoic acid; from which, by oxidation with chromic acid, γ-keto-hexahydrobenzoic acid (I.) was obtained. The ester of this acid reacts with magnesium methyl iodide, giving the lactone of γ-hydroxy-hexahydro-*m*-toluic acid (II.). When this is heated with hydrobromic acid it yields γ-bromohexahydro-*m*-toluic acid (III.), which on treatment with pyridine loses hydrobromic acid, and is changed into tetrahydro-*m*-toluic acid (IV.). After esterification, this is treated with magnesium methyl iodide and water, whereby an alcohol (V.) is produced which differs from terpineol in that the hydroxyl and methyl groups are in the 1,3-position to each other, while in terpineol they are in the 1,4-position. Just as terpineol, when treated with acid potassium sulphate, loses water to form dipentene, this new alcohol loses water and forms carvestrene (VI.):



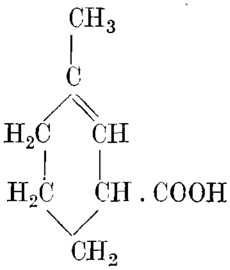
(I.)



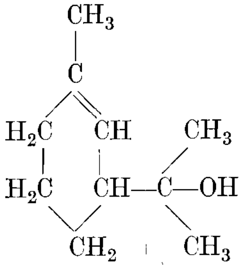
(II.)

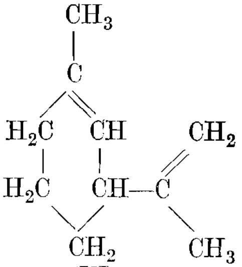


(III.)

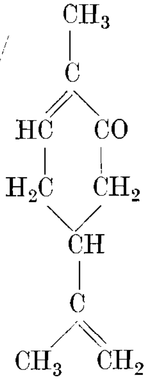


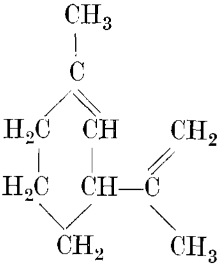
(IV.)


(V.)


(VI.)

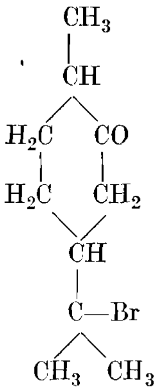
Though since the discovery of this new synthesis the old way of preparing carvestrene has lost its value as a practical method, a very brief description of it may be given here on account of one transition which occurs in the course of the reactions. The starting-point for the old synthesis was the substance carvone, which has already been encountered. Now, as can be seen from the formulæ of the two substances, to convert carvone into carvestrene the isopropylene group must be shifted from one carbon atom to the adjacent one. How this is done will be seen in due course.


Carvone.

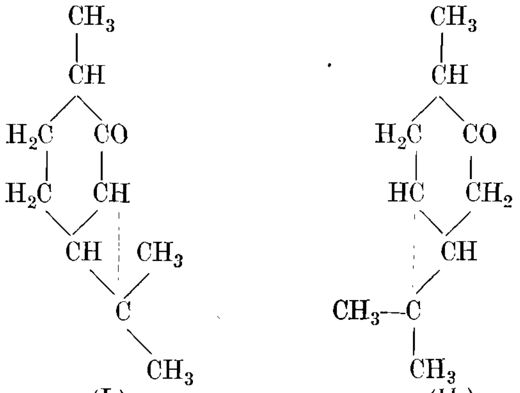

Carvestrene.

Carvone is first reduced with zinc dust and alcoholic potash to dihydrocarvone; hydrobromic acid is then added on, giving dihydrocarvone hydrobromide: *

* When a halogen acid is added on to the double bond of an unsaturated substance, the negative part (*i.e.*, the halogen atom) always unites with that carbon atom to which the *fewest* hydrogen atoms are attached. For example,

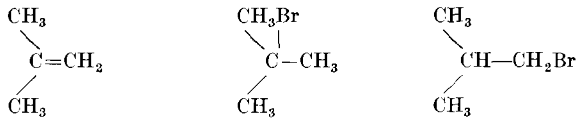


Now, when this substance is treated with alcoholic potash it gives up hydrobromic acid, but instead of regenerating a carvone derivative it yields a new ketone, carone. Since on oxidation carone yields 1, 1-dimethyl-2, 3-trimethylene dicarboxylic acid (caronic acid), it must contain a trimethylene ring. The simplest way in which this can be explained is to assume that carone has either of the formulæ (I.) and (II.)



(I.) (II.)

in the case given below the compound formed by the addition of hydrobromic acid to (I.) is (II.) and not (III.).

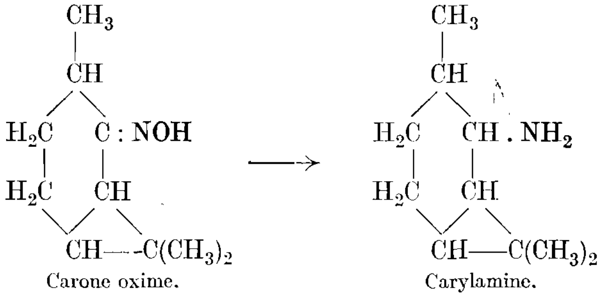


(I.) (II.) (III.)

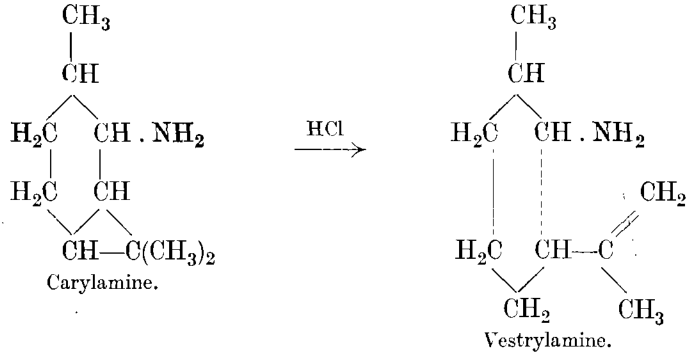
This is called the "Markownikoff Rule" (*Ber.*, 1869, **2**, 660; *Annalen*, 1870, **153**, 256). Compare, however, Cuy, *J. Amer. Chem. Soc.*, 1920, **42**, 503.

The first of these formulæ is the one usually ascribed to carone. We cannot enter into the details of the evidence here.

When carone is allowed to react with hydroxylamine it forms the substance carone oxime, which, on reduction, produces the amino-compound carylamine :



When this body is treated with alcoholic acid it undergoes isomeric change, and is converted into the hydrochloride of vestrylamine, the trimethylene ring being now broken. By this means we have transferred the isopropylene group from one carbon atom to the other.



Vestrylamine hydrochloride, on dry distillation, breaks down into carvestrene by loss of ammonium chloride :

$$C_{10}H_{17}.NH_2.HCl = C_{10}H_{16} + NH_4Cl$$

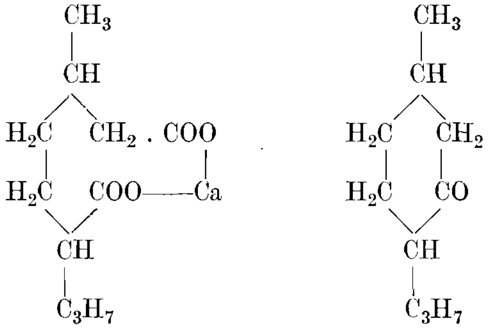
Carvestrene is a racemic compound, the dextro-antipode of which is found in nature as sylvestrene.[1] The latter has been synthesized by Perkin.[2]

[1] Baeyer, *Ber.*, 1894, **27**, 3485.
[2] Perkin, *P.*, 1910, **6**, 97.

8. *The Synthesis of Menthone*

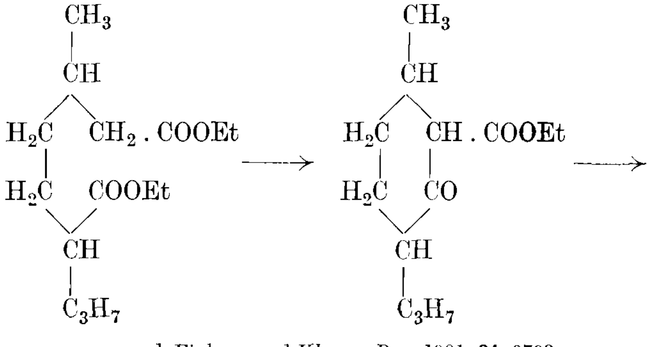
Though menthone had been synthesized in different ways by Einhorn and Klages,[1] Kötz and Hesse[2] and Haller and Martine,[3] none of these methods furnished any proof of the constitution of the substance. It was not until 1907 that synthetic evidence was obtained upon this point.

Kötz and Schwarz[4] first synthesized β-methyl-α'-isopropyl-pimelic acid, and by the distillation of its calcium salt they produced menthone :

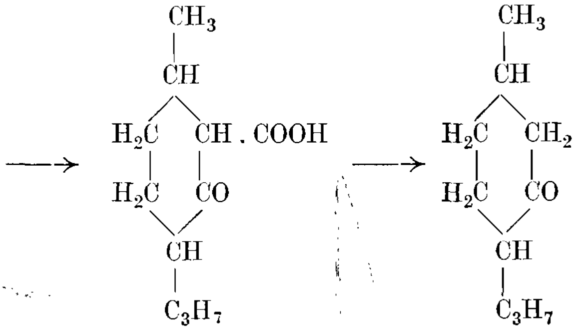


Calcium β-Methyl-α'-isopropyl-pimelate. Menthone.

A similar result is obtained by making the ester of this acid undergo intramolecular acetoacetic ester condensation by means of sodium, and then hydrolyzing the ester thus obtained and splitting off carbon dioxide in the usual way :



[1] Einhorn and Klages, *Ber.*, 1901, **34**, 3793.
[2] Kötz and Hesse, *Annalen*, 1905, **342**, 306.
[3] Haller and Martine, *Compt. rend.*, 1905, **140**, 130.
[4] Kötz and Schwarz, *Annalen*, 1907, **357**, 206.

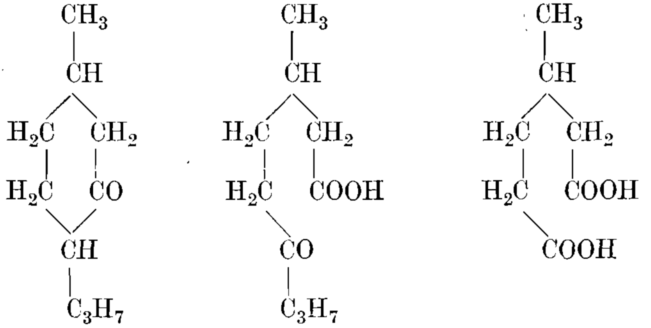


By means of this synthetic method, Kötz and Schwarz have produced an active menthone which is strongly dextro-rotatory.

9. *The Decompositions of Menthone*

Before the discovery of the syntheses which have just been described, it was not possible to show synthetically that the methyl and isopropyl radicles in menthone lay in the para-position to each other. The evidence for this had, however, been obtained from the decomposition reactions of menthone.

When menthone is oxidized by means of potassium permanganate, the first product is hydroxymenthylic acid,[1] which, on further oxidation, is converted into β-methyl-adipic acid:

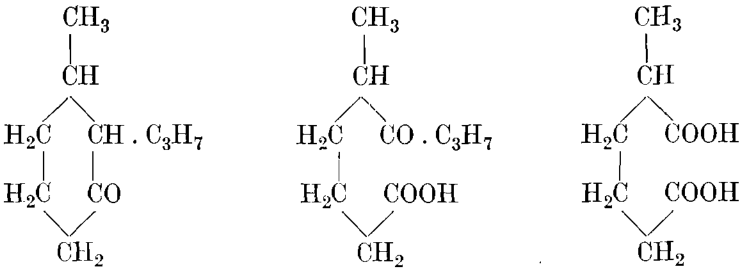


Menthone. Hydroxymenthylic acid. β-Methyl-adipic acid.

These substances could be formed only if the isopropyl and

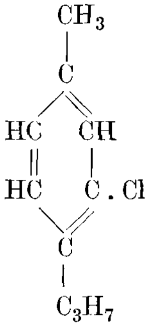
[1] Arth, *Ann. Chim. Phys.*, 1886, (vi.), **7**, 433; Beckmann and Mehrländer, *Annalen*, 1896, **289**, 367.

methyl radicles were in the para-position to each other; for if we take them in any other position, as shown below, the resulting products are not the same:



Keto-acid. α-Methyl-adipic acid.

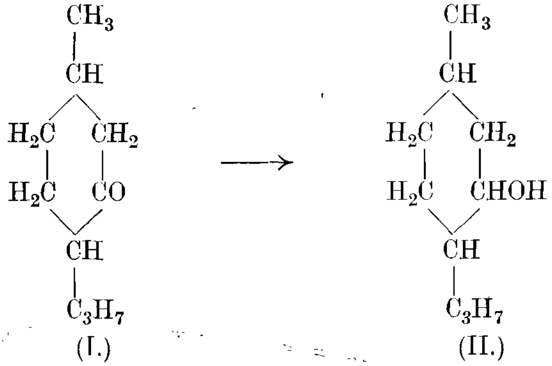
Again, the action of phosphorus pentachloride on menthone gives a dichloro-tetrahydro-cymene,[1] which, by successive treatment with bromine and quinoline, produces a chlorocymene [2] of the constitution:



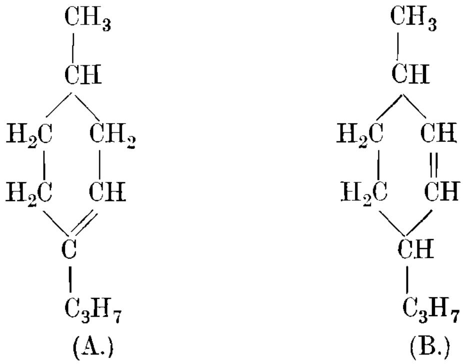
10. *The Syntheses and Constitutions of Menthol and Menthene*

Menthol is the alcohol corresponding to menthone, from which it can be prepared by reduction. Since we have established that menthone is (I.) it is obvious that menthol must be (II.):

[1] Berkenheim, *Ber.*, 1892, **95**, 694.
[2] Jünger and Klages, *Ber.*, 1896, **29**, 314.

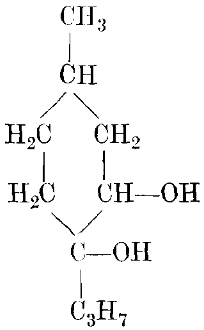


Now, when menthol is dehydrated, a hydrocarbon, *d*-menthene, is formed. This might be either (A) or (B), since water could be removed in either of two ways :

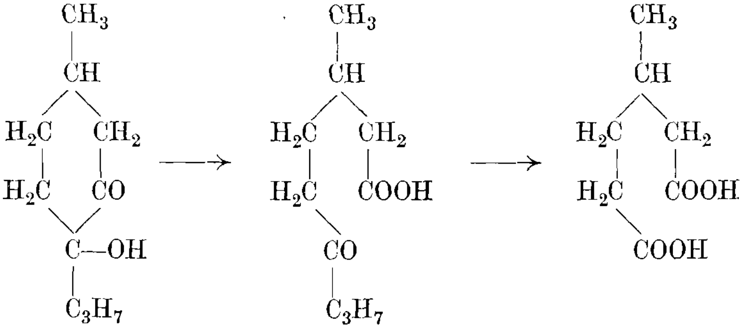


The decision between the two formulæ can be made by the aid of the evidence of the oxidation products of menthene.[1] When the menthene obtained from menthol is oxidized with potassium permanganate solution, the first product is a glycol, which, according to formula (A), would have the constitution :

[1] Wagner, *Ber.*, 1894, 27, 1639.

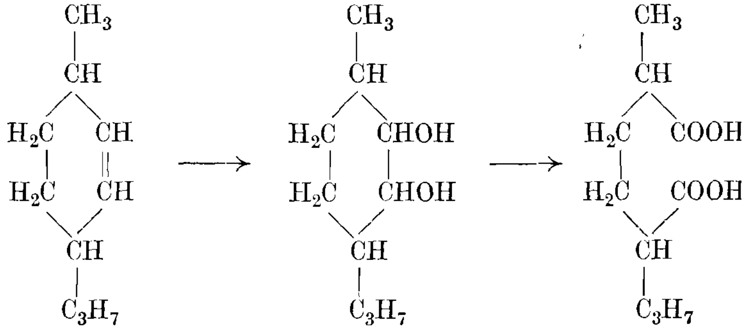


Further oxidation yields a ketone-alcohol, then hydroxy-menthylic acid, and finally β-methyl-adipic acid :

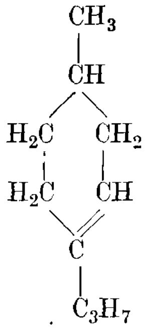


Ketone alcohol. Hydroxymenthylic acid. β-Methyl-adipic acid.

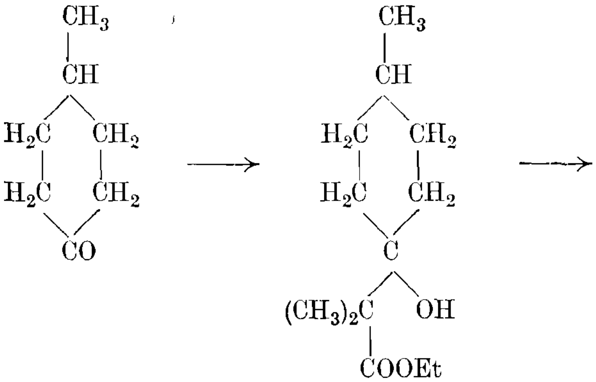
This is in agreement with the experimental results ; but if, on the other hand, we start from the second possible formula for menthene, the oxidation products would not be those found in practice, but would be the compounds shown below :



Thus the constitution of menthene must be :

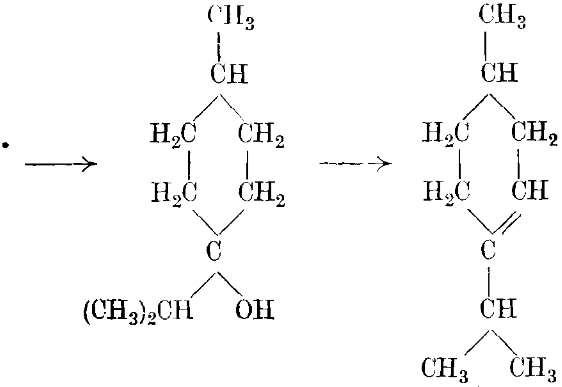


This has been confirmed by Wallach's synthesis of menthene,[1] in which he chose as his starting-point 1, 4-methylcyclohexanone (I.). This he condensed with α-bromo-isobutyric ester by means of zinc, forming (II.) ; and then, by hydrolysis and heating, caused the acid to lose carbon dioxide and become converted into an alcohol (III.), which, on boiling with sulphuric acid, lost water and yielded menthene :



(I.) (II.)

[1] Wallach, *Ber.*, 1906, **39**, 2504.

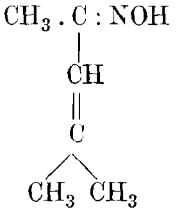


(III.) (IV.)
Menthene.

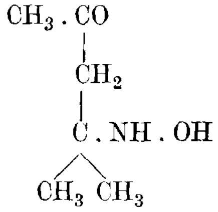
11. *The Constitution of Pulegone*

The last compound of the menthone group requiring attention here is the unsaturated ketone pulegone.

If a ketone contains a double bond in the $\alpha\beta$-position to the carbonyl group, hydroxylamine may react with it in two ways: forming an oxime in the one case, and in the other attaching itself to the double bond to give a hydroxylamine derivative. For instance, in the case of mesityl oxide, either mesityl oxime or diacetone-hydroxylamine may be produced:



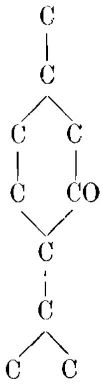
Mesityl oxime.



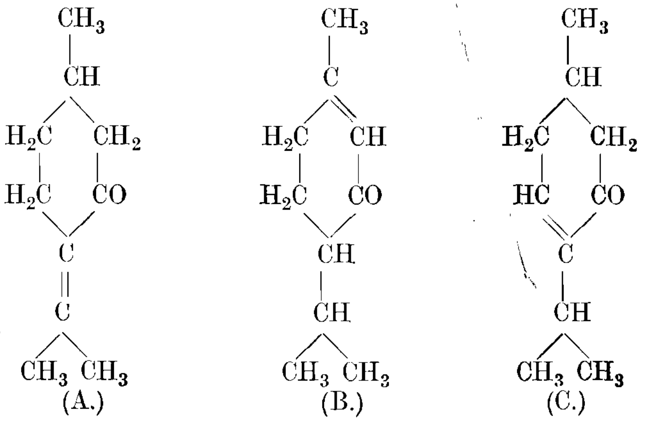
Diacetone-hydroxylamine.

Now, since pulegone shows a similar behaviour, forming either an oxime or a hydroxylamine derivative, the presumption is that it also is a ketone with an unsaturated group in the $\alpha\beta$-position to the carbonyl radicle.

Again, pulegone on reduction is converted into menthone, so that it must contain the skeleton:



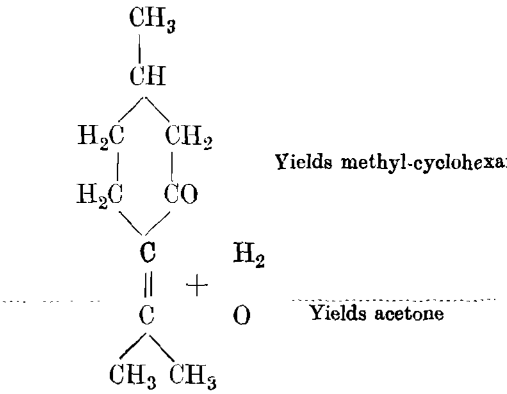
And since it has the properties of an *αβ*-unsaturated ketone it can have only three possible formulæ :



(A.) (B.) (C.)

The evidence which enables us to choose between these three has been supplied by Wallach,[1] who has shown that when pulegone is heated under pressure with water or anhydrous formic acid it undergoes decomposition into acetone and methylcyclohexanone. Since this reaction can be explained by Formula A alone, it is obvious that pulegone must have that constitution. The break-down may be formulated in the way indicated below :

[1] Wallach, *Annalen*, 1896, **289**, 337.



Yields methyl-cyclohexanone

Yields acetone

CHAPTER VIII

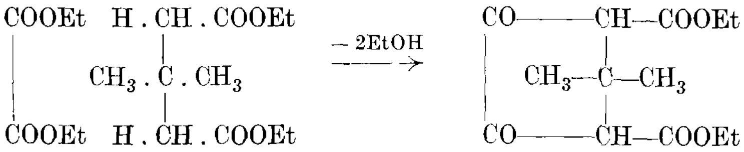
THE DICYCLIC TERPENES

A.—The Camphene-Bornylene Group

1. *Syntheses of Camphoric Acid*

In the series of dicyclic terpenes which will be described in this chapter, there are three important classes of substances. One group is derived from the hydrocarbon camphene, another from fenchene, and a third from pinene. Of these by far the most important is the camphene group. The central substance of this group is the compound camphor, $C_{10}H_{16}O$; but in order to prove the constitution of this body it will be necessary to proceed step by step, and in the first place to prove the constitution of camphoric acid, which is obtained from camphor by oxidation.

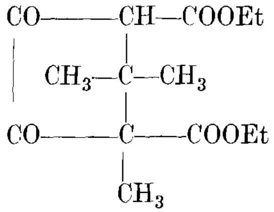
Komppa [1] and, later, Perkin and Thorpe [2] have synthesized camphoric acid. In Komppa's synthesis, the starting materials were oxalic ester and *ββ*-dimethyl-glutaric ester. These were condensed together with sodium ethylate in the usual way, producing diketoapocamphoric ester :



Diketoapocamphoric ester.

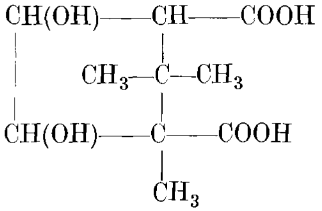
This was then methylated by means of sodium and methyl iodide, giving diketocamphoric ester :

[1] Komppa, *Ber.*, 1903, **36**, 4332 ; *Annalen*, 1909, **368**, 126 ; **370**, 209.
[2] Perkin and Thorpe, *J.*, 1906, **89**, 795.



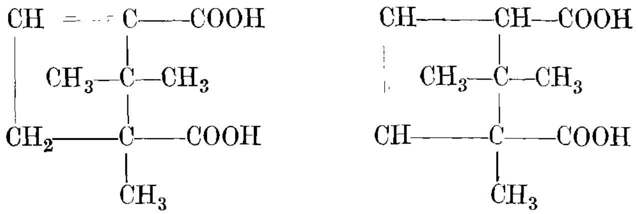
It is obvious that, since the formula is symmetrical, it makes no difference which hydrogen atom is replaced by the methyl group; the end-product in each case is the same.

This diketo-ester was dissolved in sodium carbonate solution and then treated with sodium amalgam in a stream of carbon dioxide; by this means the two carbonyl groups were reduced, and dihydroxycamphoric acid was formed, the ester being hydrolyzed by the alkaline solution:



Dihydroxycamphoric acid.

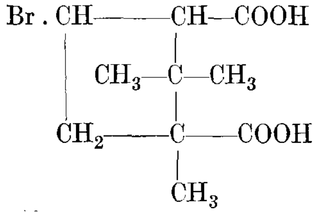
On boiling this substance with hydriodic acid in presence of red phosphorus, it was converted into dehydrocamphoric acid, which may have either of the constituents shown below:



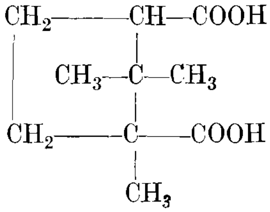
Dehydrocamphoric acid.

The constitution of this acid is of no importance, however, as the next two steps in the synthesis will yield the same final product from either of the two acids formulated above. The dehydrocamphoric acid was heated with hydrobromic acid in acetic solution to 125° C., whereby it was converted into a bromo-acid, which was then reduced with zinc dust and acetic acid to a

substance which is identical with ordinary racemic camphoric acid :



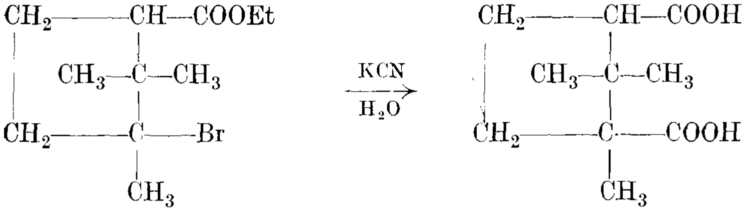
Bromo-acid.



Racemic camphoric acid.

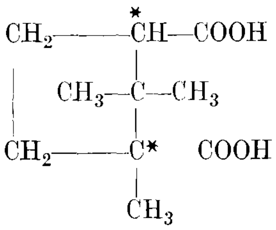
It will be seen at once that the exact constitution of the dehydrocamphoric acid is of no great importance, as the position of the bromine atom in the bromo-acid does not affect the constitution of the final camphoric acid.

The synthesis of Perkin and Thorpe started with a trimethyl-bromo-cyclopentane carboxylic ester, which was shaken with a mixture of potassium cyanide and hydrocyanic acid solutions. The resulting substance was heated and then boiled with acetic anhydride, whereby racemic camphoric anhydride was formed.

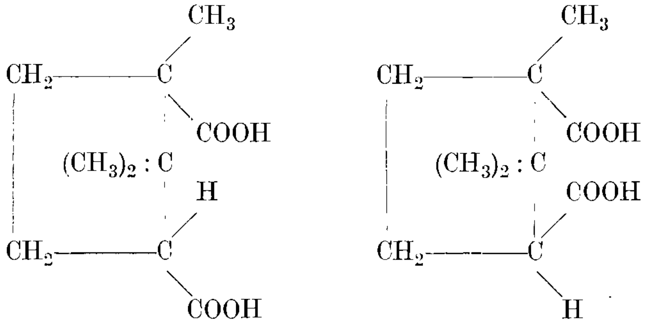


Trimethylbromo-cyclopentane carboxylic ester. Camphoric acid.

One peculiarity of camphoric acid may be pointed out here. An examination of the formula shows that camphoric acid has two asymmetric carbon atoms in its ring—these are distinguished by asterisks in the following formula :—



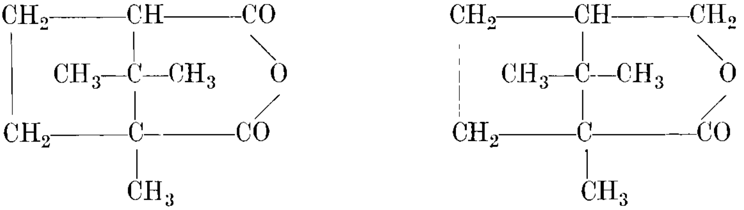
Now, when an attempt is made to racemize dextro-camphoric acid by any of the usual methods, it is found that instead of producing an equimolecular mixture of dextro- and lævo-camphoric acids the process yields merely a mixture of dextro-camphoric acid with a new substance, lævo-*iso*-camphoric acid. From this behaviour of camphoric acid it is inferred that instead of both asymmetric carbon atoms in the dextro-acid being inverted (which would yield the mirror-image lævo-camphoric) only one is altered; so that half the molecule remains as it was. The change from *d*-camphoric to *l*-*iso*camphoric would be represented thus :



d-Camphoric acid. *l*-*Iso*camphoric acid.

2. *The Synthesis of Camphor*

Camphor itself can be obtained from synthetic camphoric acid by the following method. When camphoric anhydride is treated with sodium amalgam it is reduced to campholide,[1] the reaction being analogous to the production of phthalide from phthalic acid :

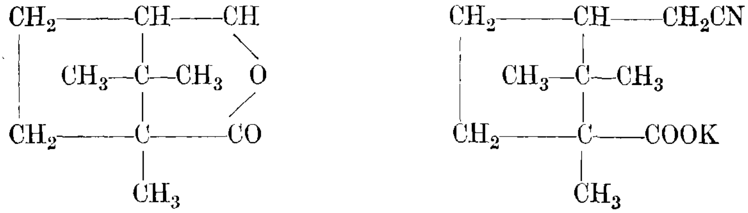


Camphoric anhydride. Campholide.

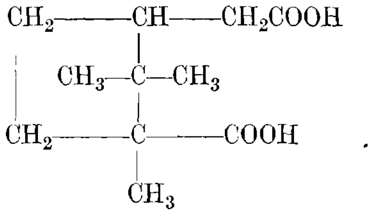
Campholide, on treatment with potassium cyanide, produces

[1] Haller, *Bull. soc. chim.*, 1896, [iii.], **15**, 7, 984 ; Forster, *J.*, 1896, **69**, 36.

a nitrile-salt, which, on hydrolysis, gives homocamphoric acid ; [1] this action is exactly like that which produces homophthalic acid from phthalide :

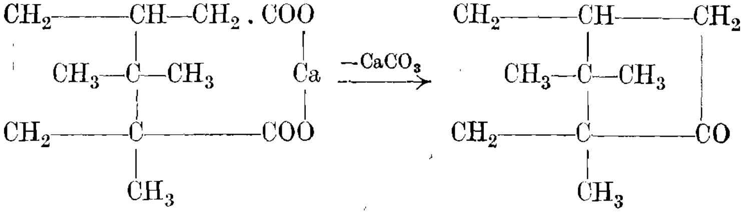


Campholide. Nitrile-salt.



Homocamphoric acid.

From this homocamphoric acid it is easy to produce camphor [2] itself by distilling the lead or calcium salt of the acid :



This synthesis confirms the camphor formula which was put forward in 1893 by Bredt.[3]

3. *Borneol and Camphane*

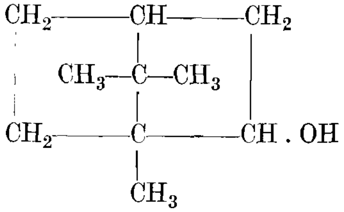
When camphor is reduced by means of sodium and alcohol [4] it yields bornyl alcohol or borneol, which has the formula :

[1] Haller and Blanc, *Compt. rend.*, 1900, **130**, 376.

[2] Haller, *Compt. rend.*, 1896, **122**, 446 ; Bredt and Rosenberg, *Annalen*, 1896, **289**, 5.

[3] Bredt, *Ber.*, 1893, **26**, 3047.

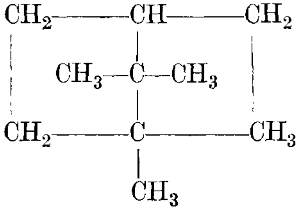
[4] Jackson and Mencke, *Am. Chem. J.*, 1883, **5**, 270 ; Wallach, *Annalen*, 1885, **230**, 225.



Borneol.

This alcohol occurs in dextro- and lævo-forms, either of which may be obtained at will by reducing the corresponding dextro- or lævo-camphor. Borneol is not the only product of this reaction, however, as at the same time a small quantity of an isomeric isoborneol [1] is produced, whose constitution is not yet definitely proved.

The hydroxyl radicle in borneol can be replaced by a halogen atom in the usual way,* and if the bornyl iodide thus formed be reduced by means of zinc dust, acetic and hydriodic acids,[2] a hydrocarbon camphane is produced, which is the root-substance of the camphor series. It has the formula :



Camphane.

4. *Bornylene*

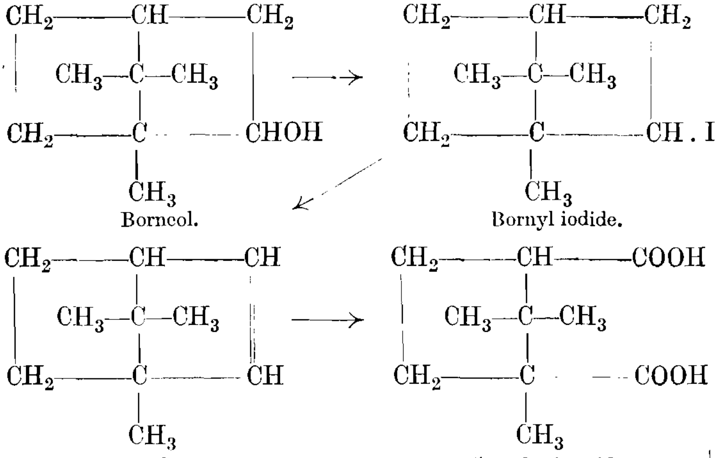
When bornyl iodide is heated with alcoholic potash to 170° it is converted into an unsaturated substance by the loss of a molecule of a halogen acid.[3] This compound, bornylene, on oxidation yields camphoric acid.

[1] Montgolfier, *Compt. rend.*, 1879, **89**, 101 ; Haller, *ibid.*, 1887, **105**, 227.

* In practice, however, bornyl iodide is usually prepared by the action of hydriodic acid on pinene, as the yields from borneol are very poor.

[2] Aschan, *Ber.*, 1900, **33**, 1006.

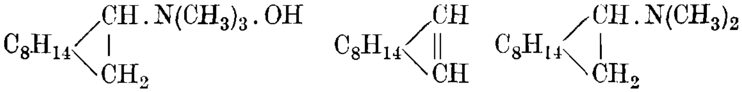
[3] Wagner and Brickner, *Ber.*, 1900, **33**, 2121.



Borneol. Bornyl iodide. Bornylene. Camphoric acid.

Bornylene therefore has the structure shown above.

Bornylene can be prepared from camphor by another method.[1] By heating camphor with ammonium formate under 60 atmospheres pressure, bornylamine was produced, from which bornyl-trimethyl-ammonium iodide was obtained. This was converted into the hydroxide (I.), which on distillation yielded a mixture of about 30 per cent. of bornylene (II.) and 60 per cent. of bornyl-dimethylamine (III.).



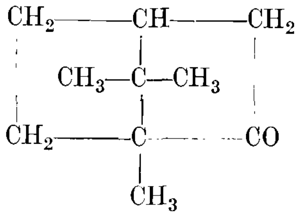
(I.) (II.) (III.)

5. *The Decomposition Products of Camphor*

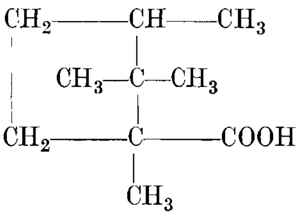
Let us now return to the problem of camphor. The most vulnerable point in the camphor molecule is the carbonyl group and the adjacent methylene radicle. The ring at this point is so easily attacked that it may be broken by a simple hydrolytic reaction. If camphor be heated with sodium and xylene to a temperature of 280° C., the ring opens ; and when the reaction mixture is poured into water, the sodium salt of campholic acid [2] is formed :

[1] Rica, *Helv. Chim. Acta*, 1920, **3**, 748.

[2] Malin, *Annalen*, 1868, **145**, 201 ; Kachler, *ibid.*, 1872, **162**, 259.

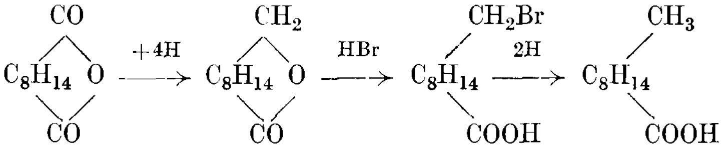


Camphor.



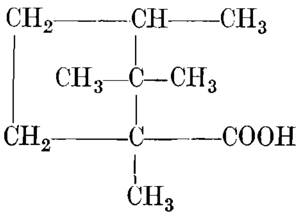
Campholic acid.

The same acid has been obtained by Haller and Blanc [1] from campholide, a method of synthesis which establishes the constitution of the substance beyond doubt :

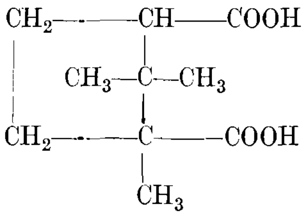


Camphoric anhydride. Campholide. Bromocampholic acid. Campholic acid.

Now, when campholic acid is oxidized with nitric acid, the newly formed methyl group is oxidized to carboxyl, and camphoric acid is formed :

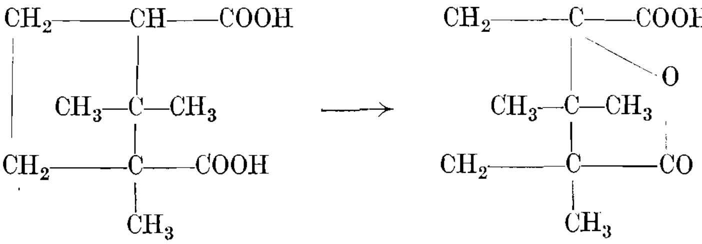


Campholic acid.



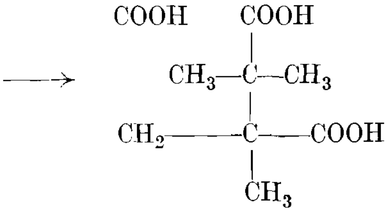
Camphoric acid.

Further action of nitric acid upon the latter substance gives rise to camphanic acid, which is oxidized in its turn to camphoronic acid :



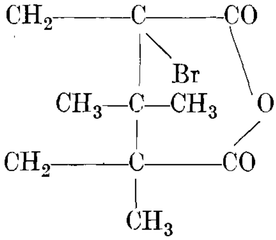
Camphoric acid. Camphanic acid.

[1] Haller and Blanc, *Compt. rend.*, 1900, **130**, 376.

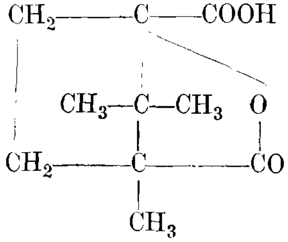


Camphoronic acid.

The constitution of camphanic acid [1] is proved by the fact that it can be obtained from bromocamphoric anhydride by boiling with water :

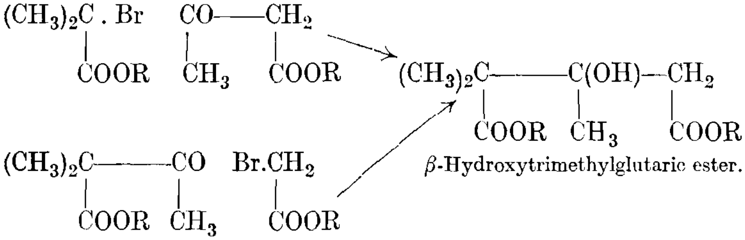


Bromocamphoric anhydride.



Camphanic acid.

The constitution of camphoronic acid was established by the synthesis of Perkin and Thorpe.[2] These authors first prepared β-hydroxy-trimethyl-glutaric ester by the action of zinc upon a mixture of acetoacetic ester and α-bromo-isobutyric ester, or upon a mixture of dimethyl-acetoacetic ester and monobromacetic ester—

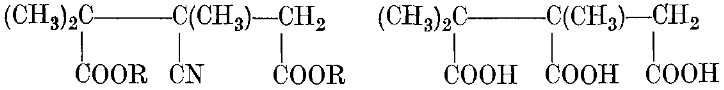


β-Hydroxytrimethylglutaric ester.

By replacing the hydroxyl group first with chlorine and then by cyanogen they obtained the nitrile ester of camphoronic acid, from which the acid itself was produced by hydrolysis—

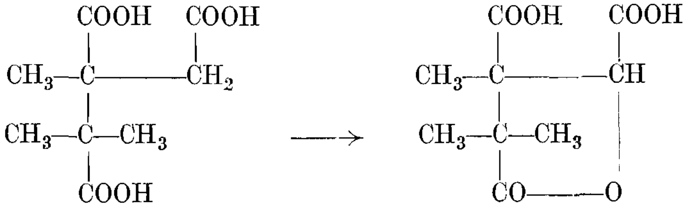
[1] Reyher, "Dissertation," Leipzig, 1891; Bredt, *Ber.*, 1894, **21**, 2097; Lapworth and Lenton, *J.*, 1902, **81**, 17.

[2] Perkin and Thorpe, *J.*, 1897, **71**; 1169.

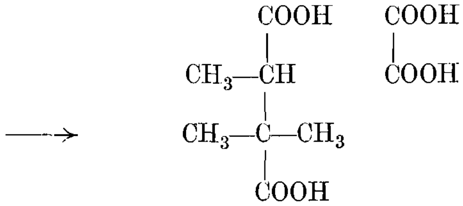


Camphoronic nitrile. Camphoronic acid.

When camphoronic acid is heated to above 135° C., it loses water and is converted into anhydrocamphoronic acid, $C_9H_{12}O_5$. By brominating the chloride of this acid, two isomeric bromo-anhydrocamphoronic chlorides are produced, one of which, when boiled with water, gives the lactone of an unstable hydroxy-camphoronic acid (camphoranic acid), while the other yields stable hydroxycamphoronic acid. Camphoranic acid, when fused with potash, breaks down into oxalic and trimethyl-succinic acids.[1] These changes may be expressed thus :



Camphoronic acid. Camphoranic acid.



Trimethylsuccinic and oxalic acids.

6. *Camphene.*

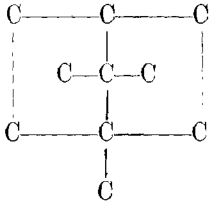
Camphene, $C_{10}H_{16}$, is a hydrocarbon isomeric with bornylene ; but its constitution is still one of the enigmas of organic chemistry. It would occupy too much space were we to weigh the pros and cons of all the formulæ which have been proposed for the compound ; and in the present section we can do little more than indicate the difficulties with which the problem is surrounded.[2]

[1] Bredt, *Annalen*, 1898, **299**, 150.

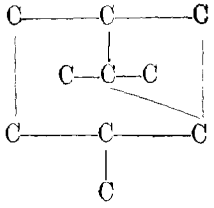
[2] For recent discussions of camphene's structure see Aschan, *Annalen*, 1910, **375**, 336 ; Lipp, *ibid.*, 1911, **382**, 265 ; Henderson and Heilbron, *J.*, 1911, **99**, 1901.

In the first place, mention may be made of two methods by which the hydrocarbon can be produced,* as these show how complex the question is, even in its earliest stages.

Berthelot [1] prepared it by heating pinene hydrochloride or hydrobromide with sodium stearate to 200°–220° C. Wallach [2] obtained it by dehydrating borneol with potassium bisulphate at 200° C. or by heating bornyl chloride with aniline. It has been shown above that bornylene contains the skeleton (I.), and, as will be seen later, the pinene molecule contains the skeleton (II.)



(I.)



(II.)

so that even at this stage some intramolecular change must be assumed during the formation of camphene from one or other of these groupings. Once the camphene skeleton is formed, it is extremely stable. Those reagents which usually produce intramolecular rearrangement act upon it only at high temperatures, and their effect is to bring about deep-seated changes in its structure.

When camphene is treated with bromine, the first reaction appears to be an addition of one molecule of the halogen; but this is immediately followed by a separation of hydrobromic acid, leaving a mono-bromocamphene.[3] By further action of bromine or by brominating camphene in ligroin solution at —10° C., a halogen addition product, camphene dibromide,[4] is obtained which has the composition $C_{10}H_{16}Br_2$. A tribromide, $C_{10}H_{16}Br_3$, has also been obtained, which is probably formed partly by substitution and partly by addition.

Concentrated nitric acid forms with camphene an addition

* Crude "camphene" appears to contain materials other than pure camphene (Aschan, *Annalen*, 1910, **375**, 336).

1 Berthelot, *Compt. rend.*, 1862, **55**, 496.

2 Wallach, *Annalen*, 1885, **230**, 233, 239.

3 Wallach, *Annalen*, 1885, **230**, 233.

4 Reychler, *Ber.*, 1896, **29**, 900.

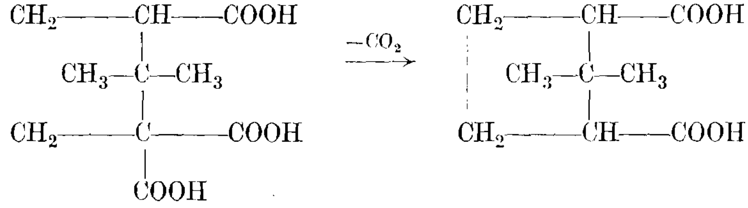
product containing equimolecular quantities of the two reagents.[1]

Hydrochloric acid acts upon camphene giving the chloride of an alcohol, isoborneol; whilst a mixture of sulphuric acid and acetic acid produces with camphene the acetate of the same alcohol.[2]

By the action of nascent nitrous acid upon camphene,[3] three compounds are simultaneously formed: camphene nitronitrosite, $C_{10}H_{16}(NO_2)_2 . NO$; camphene nitrosite, $C_{10}H_{16} . (NO_2) . NO$; and camphenylnitrite, $C_{10}H_{15} . O . N : O$. When the last compound is heated with potassium hydroxide solution it yields a ketone, camphenilone, $C_9H_{14}O$; whilst on reduction it produces camphenilan aldehyde, $C_9H_{15} . CHO$. The same aldehyde is formed from camphene by the action of chromyl chloride and hydrolysis with water.[4]

Oxidation of camphene with alkaline permanganate[5] produces an 80 per cent. yield of camphenic acid.

When nitric acid[6] is substituted for permanganate, the first product isolated is camphoic acid, a tribasic acid which on heating loses carbon dioxide and produces apocamphoric acid. This reaction recalls the behaviour of malonic acid; and the constitution of camphoic acid is therefore assumed to be that which is shown below:—



Camphoic acid. Apocamphoric acid.

Camphoic acid is also obtained by the oxidation of dihydrocamphene.[7]

[1] Bouveault, *Bull. soc. chim.*, 1900, (3), **23**, 533.
[2] Bertram and Wahlbaum, *J. pr. Chem.*, 1894, (2), **49**, 8.
[3] Jagelki, *Ber.*, 1899, **32**, 1501.
[4] Bredt and Jagelki, *Annalen*, 1900, **310**, 112.
[5] Haworth and King, *J.*, 1912, **101**, 1975.
[6] Marsh and Gardner, *J.*, 1891, **59**, 64; 1896, **69**, 74.
[7] Lipp, *Annalen*, 1911, **382**, 265.

Henderson and Sutherland [1] obtained, among the oxidation products of camphene, isocamphenilan aldehyde (supposed to be a stereoisomer of camphenilan aldehyde), camphenilone, and an acid $C_{10}H_{16}O_2$, isomeric with isocamphenilanic acid, into which it is transformed by heating with acetic anhydride. When acted upon by chromic acid, camphene is converted into camphor.[2] The ozonide of camphene yields on decomposition formaldehyde, camphenilone, and dimethyl-norcampholide.

Finally, Henderson and Pollock [3] have shown that when camphene is reduced by Sabatier and Senderens' method it yields, not camphane, but an isomeric hydrocarbon.

We must now see how far this evidence takes us.

In the first place, it is clear that the syntheses of camphene throw no great light upon its constitution. Either the production of camphene from borneol or its formation from pinene hydrochloride must entail a molecular rearrangement, since these substances do not contain the same skeleton; and it is not impossible that both reactions are attended by intramolecular change.

The reaction between camphene and bromine brings us a stage further. Ethylene derivatives sometimes react in this way, when at least one of the carbon atoms joined by the double bond carries a hydrogen atom. Further, the ready action of the halogen in the case of camphene leads to the conclusion that it probably contains some grouping such as $R_2 : C : CH_2$ or $R_2 : C : CHR$; since these are more readily attacked than the parent hydrocarbon. The possibility that the action of bromine is due to the presence of an easily-opened polymethylene ring in the camphene structure appears to be negatived by the reaction between the hydrocarbon and nitrous acid, which implies the presence of an ethylenic bond.

The behaviour of camphenyl nitrite with caustic potash points to its probably having the structure $C_9H_{14} : CH . O . N : O$; which would indicate that camphene itself contains the group $R_2C : CH_2$.

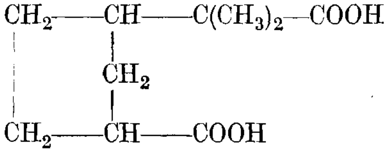
It is now necessary to gain information with regard to the

[1] Henderson and Sutherland, *J.*, 1911, **99**, 1539.

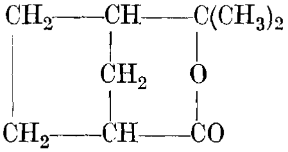
[2] Armstrong and Tilden, *Ber.*, 1879, **12**, 1756.

[3] Henderson and Pollock, *J.*, 1910, **97**, 1620; compare Lipp, *Annalen*, 1911, **382**, 265.

position of the two methyl groups; and the syntheses of camphenic acid[1] and dimethyl-norcampholide[2] supply the required material. From the structures of these compounds shown below it will be seen that the two methyl groups are attached to a carbon atom outside the pentamethylene ring.

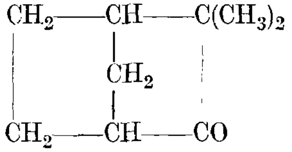


Camphenic acid.

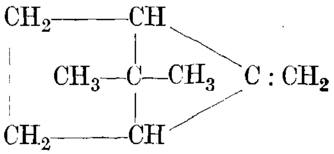


Dimethyl-norcampholide.

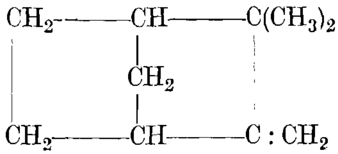
Again, camphenilone has been synthesized[3] and shown to have the structure:



This evidence excludes the Semmler formula for camphene:



So far, then, the experimental evidence points towards the Wagner formula:



but it must be admitted that even this formula will not fit all the facts. It is difficult to see how the production of camphenic acid can be accounted for directly.

The only solution is to assume that intramolecular changes occur in the camphene molecule under the action of various

[1] Lipp, *Ber.*, 1914, **47**, 871.
[2] Komppa and Hintikka, *Ber.*, 1909, **42**, 898.
[3] Komppa and Hintikka, *Ber.*, 1914, **47**, 1550.

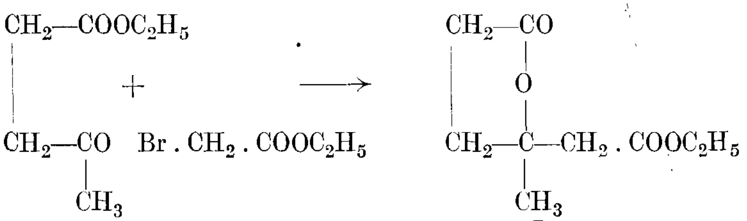
reagents ; and, as will be seen in the last section of this chapter, some such intramolecular rearrangements must be postulated if the behaviour of this group of terpenes is to be explained in a satisfactory manner.

B.—Fenchene and its Derivatives

1. *The Syntheses of Fenchone and Fenchyl Alcohol*

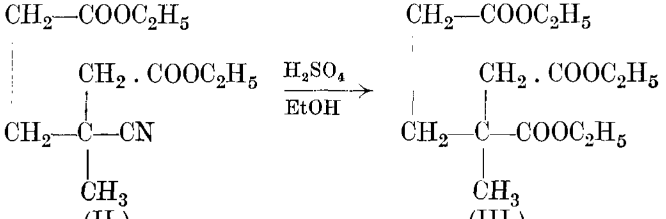
For many years the exact constitution of fenchone had not been placed beyond doubt; for its degradation products are labile and difficult to utilize in the problem of determining the structure of the parent compound. A synthesis of the substance has now been attained, however, which establishes its constitution.[1]

The actual synthesis started from lævulinic ester and bromacetic ester which were condensed together by means of zinc :



(I.)

The lactonic ester (I.) thus formed was heated with potassium cyanide, which converted it into the nitrile (II.). By means of concentrated sulphuric acid and alcohol, the nitrile is made to yield the tri-ester (III.).

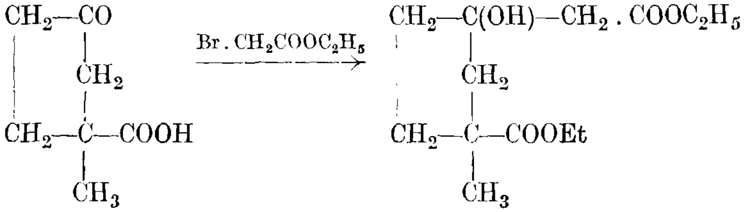


(II.) (III.)

On heating with sodium and benzene, this substance formed a pentamethylene derivative (IV.) ; and when the ethyl ester of

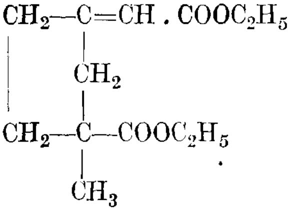
[1] Ruzička, *Ber.*, 1917, **50**, 1362.

this was condensed with α-bromoacetic ester in presence of zinc, a new chain was added, as shown in (V.). This compound apparently lost water and formed (VI.); for the reaction mixture contained both materials :



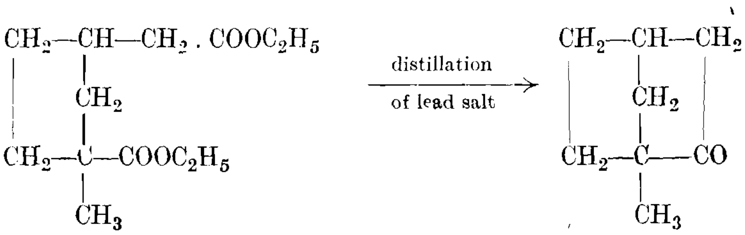
(IV.) (V.)

and



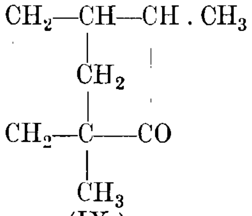
(VI.)

The mixture was treated with phosphorus tribromide in chloroform, which converted it all into (VI.); and then the ester was reduced to (VII.). The lead salt of this broke down on distillation in the usual manner, forming the internal ketone, methyl*nor*camphor (VIII.).

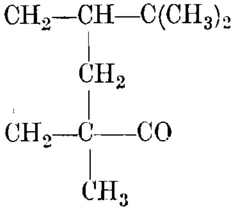


(VII.) (VIII.)

Methylation by means of sodamide and methyl iodide completed the process, producing a mixture of fenchosantenone (IX.) and racemic fenchone :



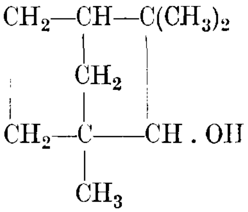
(IX.)



Fenchone.

This synthesis proved the correctness of the formula proposed for fenchone by Semmler.[1]

Reduction of fenchone produces fenchyl alcohol, which must therefore have the following structure :—



Fenchyl alcohol.

2. *The Decompositions of the Fenchenes*

For a long time the structures of the fenchenes were a puzzle to organic chemists. As has been seen, the reduction of fenchone yields fenchyl alcohol. It is found that *d*-fenchone gives rise to a lævo-rotatory alcohol, which is therefore described as D-*l*-fenchyl alcohol. When this is treated with phosphorus pentachloride at a low temperature it gives D-*l*-fenchyl chloride which, with aniline, loses hydrochloric acid and yields D-*l*-fenchene. This compound is now known as α-fenchene.[2]

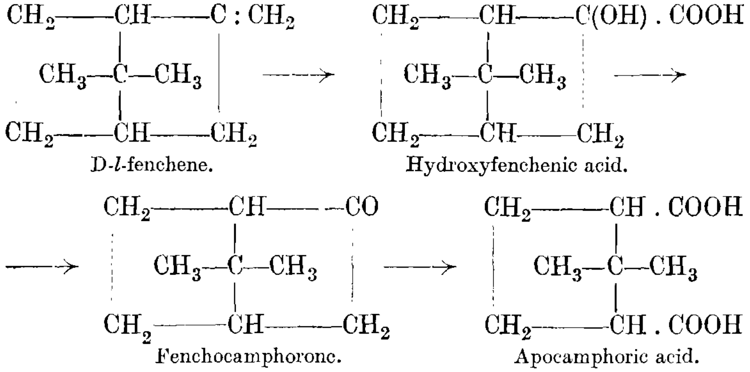
If phosphorus pentachloride be allowed to act on fenchyl alcohol without cooling, a dextro-rotatory chloride is formed, which on treatment with aniline, produces D-*d*-fenchene, or β-fenchene. It is also possible to prepare β-fenchene by heating fenchyl alcohol with potassium hydrogen sulphate.[2]

The constitution of D-*l*-fenchene (α-fenchene) has been

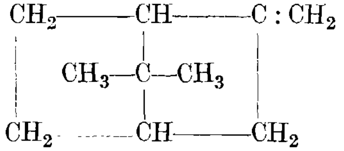
[1] Semmler, *Ch. Ztg.*, 1905, **29**, 1313 ; compare Bouveault and Levallois, *Compt. rend.*, 1908, **146**, 180.

[2] Komppa and Roschier, *Ann. Acad. Sci. fennicæ*, 1915, (A), **7**, No. 14, 1.

dealt with in the following way.[1] When it is oxidized with potassium permanganate it is converted into a hydroxy-acid, D-*l*-hydroxy-fenchenic acid, which has the composition $C_{10}H_{16}O_3$. This body, when treated with lead peroxide and sulphuric acid, loses carbon dioxide and two atoms of hydrogen, being converted into D-*d*-fenchocamphorone, $C_9H_{14}O$. By nitric acid, this last compound is broken down to apocamphoric acid. This production of apocamphoric acid from fenchene shows that in fenchene itself one of the carbon atoms must be attached to the nucleus at a point different from that at which the methyl group in camphor is placed; as otherwise camphoric acid would be produced in the end instead of its next lower homologue, apocamphoric acid. The only way in which we can satisfy this requirement is shown in the formulæ below:



D-*l*-fenchene, therefore, has the constitution expressed by:



How such a structure can arise by the dehydration of fenchyl alcohol or the removal of a molecule of hydrochloric acid from fenchyl chloride, is one of the puzzles of organic chemistry; and the matter is not made simpler by the occurrence of the second fenchene isomer.

With regard to the constitution of this β-fenchene, very

[1] Wallach, *Annalen*, 1898, **300**, 294; 1901, **315**, 283.

little is known.[1] When prepared from racemic fenchyl alcohol and sodium hydrogen sulphate, it forms part of a mixture of hydrocarbons from which it can be separated by distillation. The pure product, on oxidation with alkaline permanganate, yields *r*-hydroxy-*β*-fenchenic acid, isomeric with hydroxy-fenchenic acid. Further oxidation, with acid permanganate, gives *r*-*β*-fenchocamphorone, isomeric with fenchocamphorone; and a final oxidation, this time with alkaline permanganate, produces a dibasic acid, $C_9H_{14}O_4$, an isomer of apocamphoric acid. This last compound gives no anhydride, which may point to it being a *trans*-compound. Beyond that, nothing is known of its structure.

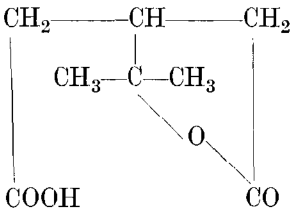
C.—Pinene

1. *The Constitution of Pinene*

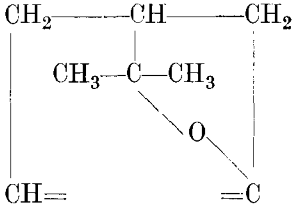
Pinene is a hydrocarbon isomeric with camphene and fenchene. It was found by Sobrero[2] that when this substance was allowed to stand in sunlight in contact with water and air it was, after several months, converted into a compound sobrerol,* $C_{10}H_{16}(OH)_2$, which, on boiling with dilute acids, was changed, by the loss of one molecule of water, into pinol, $C_{10}H_{16}O$. Pinol was found, on further investigation, to be an internal ether of the same type as cineol. Wallach[3] showed that pinol may also be obtained by the action of sodium ethylate on terpineol dibromide.

When pinol or sobrerol is treated with a 1 per cent. solution of potassium permanganate the product is a dihydric alcohol[4] pinol-glycol, $C_{10}H_{16}O(OH)_2$. On further oxidation, a tetra-hydric alcohol[5] sobrerythrite, $C_{10}H_{16}(OH)_4$, is formed, which in turn is oxidized to terpenylic acid. Therefore we should find in pinene, pinol, and pinol-glycol, the same chain of carbon atoms which we know exists in terpenylic acid :

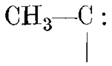
[1] Komppa and Roschier, *Ann. Acad. Sci. fennicæ*, 1915, (A), 7, No. 14, 1.
[2] Sobrero, *Annalen*, 1861, **80**, 106.
* Sobrerol can also be obtained by acting on pinene with mercuric acetate (Henderson and Agnew, *J.*, 1909, **95**, 289).
[3] Wallach, *Annalen*, 1890, **259**, 309.
[4] Wagner and Slawinski, *Ber.*, 1894, **27**, 1644.
[5] Wagner and Ginsberg, *Ber.*, 1894, **27**, 1648; 1896, **29**, 1195.



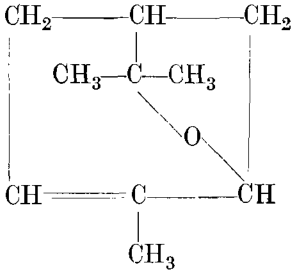
In other words, the pinol skeleton must contain the grouping :



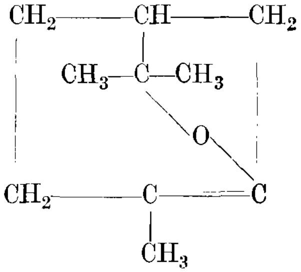
Into this scheme we have now to fit a hydrogen atom and the group :



and, as can at once be seen, there are two possible ways of doing this :

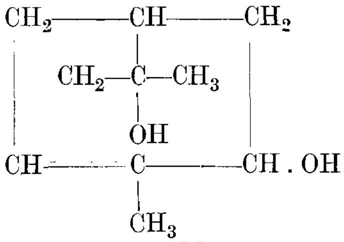


Pinol I.

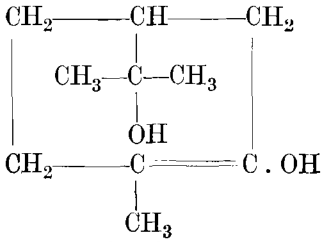


Pinol II.

On these two assumptions sobrerol, which is obtained from pinol by the addition of water, would have either of the formulæ :

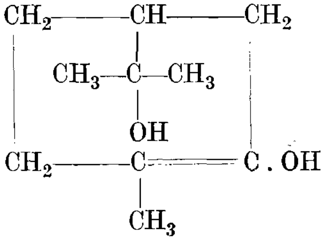


Sobrerol I*a*.

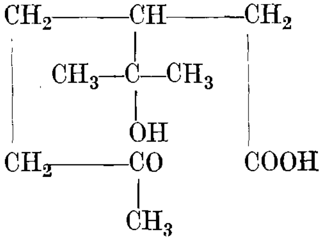


Sobrerol II*a*.

Now, sobrerol, on oxidation with a 1 per cent. solution of potassium permanganate, gives a tetrahydric alcohol, sobrerythrite. This can only be explained by using the formula (I*a.*), for (II*a.*) would produce a hydroxy-ketone :



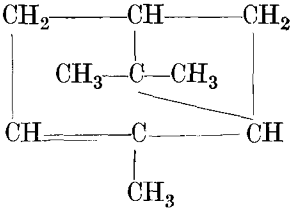
Sobrerol II*a.*



Hydroxy-ketone.

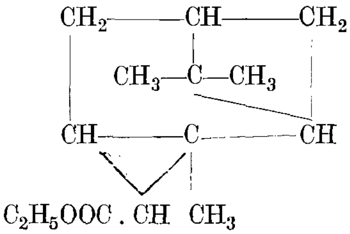
Sobrerol, therefore, has the formula (I*a.*) and pinol the formula (I.).

From this we may conclude that the formula of pinene itself is:



Pinene.

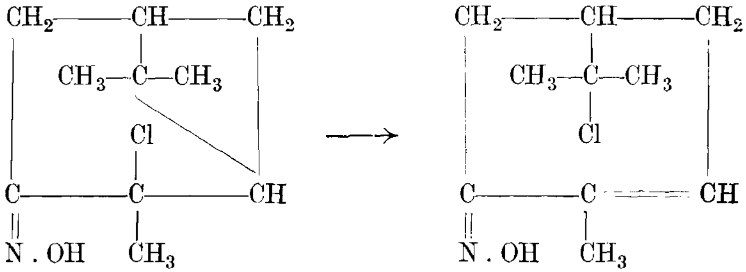
Further evidence in support of this constitution is supplied by the behaviour of pinene with diazo-acetic ester. It is well known that the latter body interacts with compounds containing ethylenic bonds to produce pyrazolin derivatives, which then decompose, yielding trimethylene compounds.[1] Now when pinene and diazo-acetic ester interact, the end-product is a substance of the following structure [2] :—



[1] Buchner and Curtius, *Ber.*, 1885, **18**, 237.
[2] Buchner and Rehorst, *Ber.*, 1913, **46**, 2680, 2687.

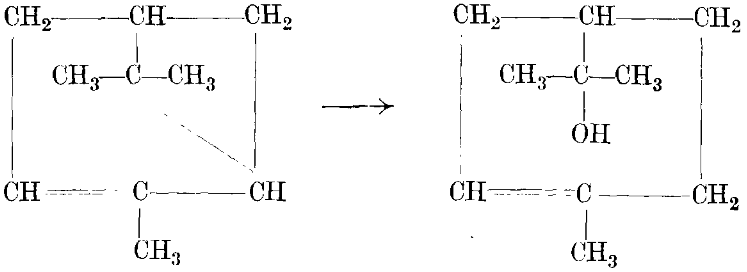
and since we know that the ring is formed partly from the two atoms between which the double bond originally existed, this tends to establish the pinene formula which was deduced above.

In virtue of the double bond in its molecule, pinene is capable of uniting with hydrochloric acid or nitrosyl chloride. Pinene hydrochloride resembles camphor in appearance and smell, and is used commercially under the name of "artificial camphor." Pinene nitrosochloride,[1] on standing in presence of hydrochloric acid, is converted into hydrochlorocarvoxime by the wandering of a chlorine atom and the rupture of the pinene tetramethylene ring:



Pinene nitrosochloride. Hydrochlorocarvoxime.

Pinene itself is converted into terpineol by hydration with dilute acids :



Pinene. Terpineol.

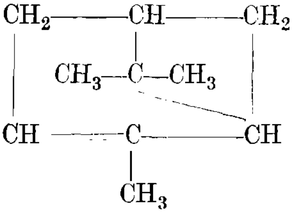
[1] Baeyer, *Ber.*, 1896, **29**, 20.

2. *Pinonic and Pinic Acids*

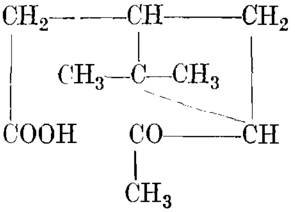
When pinene is oxidized with potassium permanganate, the first product is a ketonic acid[1] which, according to the conditions of the experiment, can be obtained either as a single substance or as a mixture of two isomers. When the single substance is produced it is found to have the composition $C_{10}H_{16}O_3$, and has been named α-pinonic acid. It contains the group CH_3-CO-, for, on treatment with bromine and potash, it loses a methyl group, takes up hydroxyl, and is converted into pinic acid, $C_9H_{14}O_4$.

$$\underset{\text{Pinonic acid.}}{C_8H_{13}O_2—CO—CH_3} \xrightarrow{\text{KOH and Br}} \underset{\text{Pinic acid.}}{C_8H_{13}O_2—COOH} + CH_3Br$$

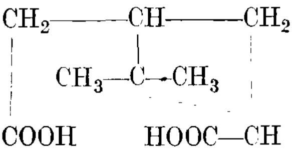
These changes are expressed in the following formulæ :—



Pinene.



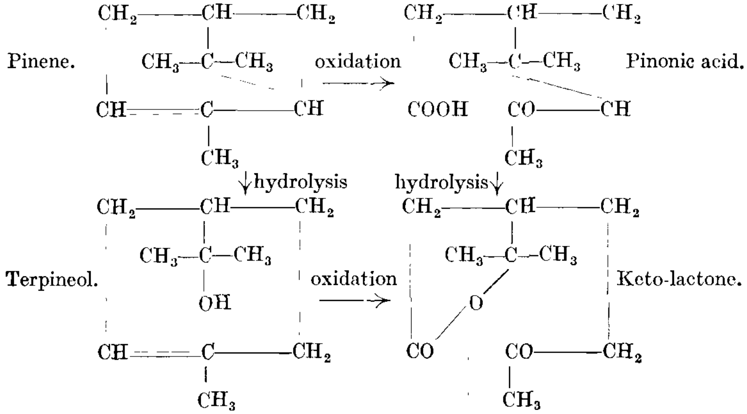
Pinonic acid.



Pinic acid.

Now, on hydrolysis with 50 per cent. sulphuric acid pinonic acid gives a keto-lactone,[2] $C_{10}H_{16}O_2$, which proves to be identical with that obtained in the oxidation of terpineol. A similar hydrolysis converts pinene into terpineol, so that the following scheme shows the relations between the four substances :—

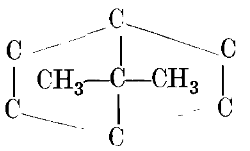
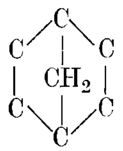
[1] Baeyer, *Ber.*, 1896, **29**, 3. [2] Baeyer, *Ber.*, 1896, **29**, 3.



D.—Intramolecular Rearrangements in the Dicyclic Terpenes

It has already been pointed out in the course of this chapter that some of the reactions in the dicyclic terpene group cannot be satisfactorily represented without the aid of assumed intramolecular changes. Some suggestions as to the nature of such changes have been made by Aschan [1] and Meerwein; [2] while Collie [3] has worked out a more complete scheme which may now be outlined.

In order to account for the intramolecular changes proposed, three assumptions are made. In the first place, it is assumed that a trimethylene ring may be formed or ruptured within the molecule. Secondly, it is postulated that a dicyclic compound containing two five-membered rings is more stable than an isomer which contains one four-membered and one six-membered ring. Thirdly, the suggestion is made that the grouping (I.) is preferred to (II.) in the course of intramolecular changes.

(I.)   (II.)

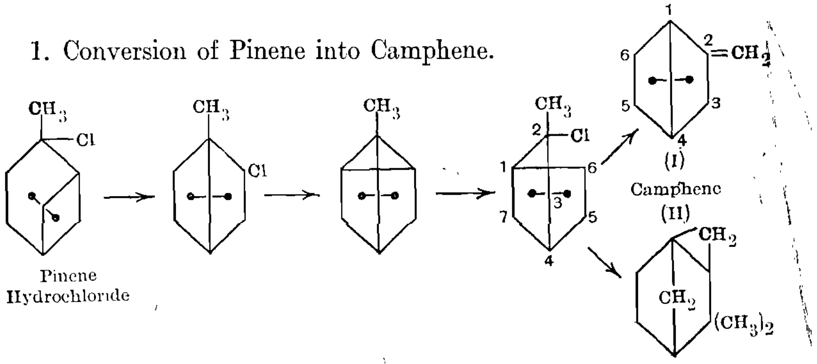
[1] Aschan, *Annalen*, 1912, **387**, 1.
[2] Meerwein, *ibid.*, 1914, **405**, 129.
[3] Collie, private communication.

Now let us take the changes in the camphene series as a starting-point. The scheme of these is given below.

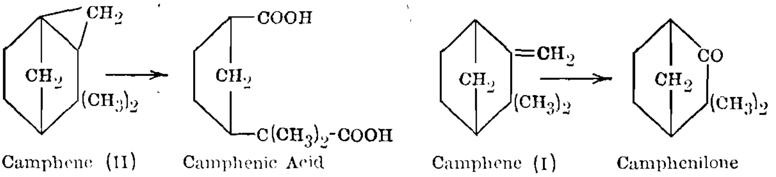
Camphene's Reactions

(Note : The symbol •—•—• is used to represent CH_3—C—CH_3 inside the hexagon.)

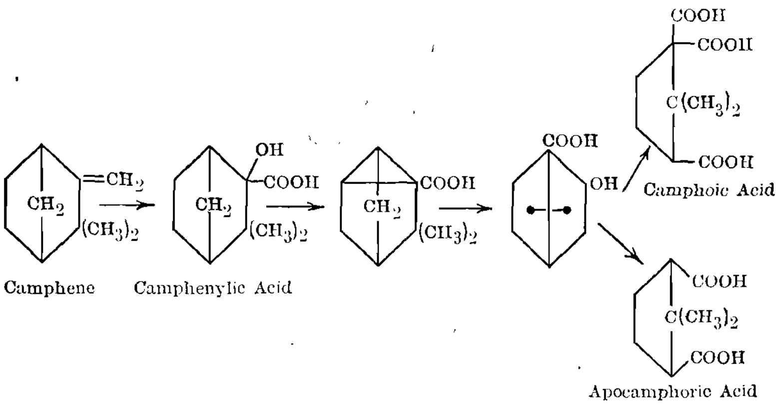
1. Conversion of Pinene into Camphene.



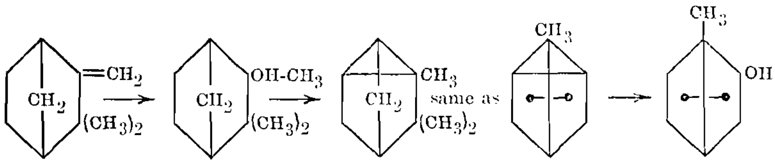
2. Formation of Camphenic Acid and Camphenilone.



3. Camphoic Acid and Apocamphoric Acid from Camphene.



4. Production of Bornyl Alcohol from Camphene.



Camphene Bornyl Alcohol

The first set of changes is concerned with the conversion of pinene hydrochloride into camphene. It will be noticed that the initial step depends upon the third assumption and requires a rearrangement of the grouping (II.) into the grouping (I.), which is accompanied by a wandering of the chlorine atom from one carbon atom to the next. The next two stages represent the splitting off of hydrochloric acid with the formation of a trimethylene ring and the subsequent readdition of the acid in a new position to give two pentamethylene rings. Finally, by the elimination of hydrochloric acid, camphene is formed, which may be represented either according to the Wagner formula or with a trimethylene ring in its system, these two structures being assumed to be mutually interchangeable.*

The second series of rearrangements is based upon this view of the duality of the camphene structure. The trimethylene ring variety gives rise to camphenic acid; whilst the Wagner formula leads to camphenilone.

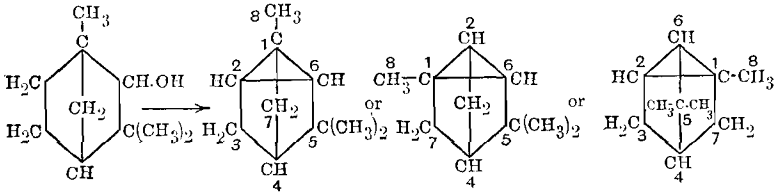
The production of camphoic acid and apocamphoric acid is dealt with in the third series. In this case, the first step is the production of a hydroxy-acid by the gentle oxidation of the double bond in the camphene molecule. Then follows the elimination of water and the formation of a trimethylene ring. By the readdition of water, this trimethylene ring is opened; and the fission takes a form which brings into existence the grouping (I.) instead of the grouping (II.). Finally, oxidation gives rise to camphoic and apocamphoric acids.

The fourth series of changes shows the conversion of camphene into bornyl alcohol. The first step is the addition of a molecule of water. Then follows elimination of water from a different pair of positions, with the production of the trimethylene ring.

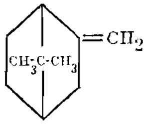
* For a somewhat parallel rearrangement, compare the conversion of dihydrocarvone into carone or the change of carylamine into vestrylamine, etc.

The next formula is identical but is merely written in a different form. Finally, the trimethylene ring is ruptured by the addition of water and bornyl alcohol is produced.

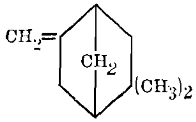
Let us now turn to the fenchene series. Collie symbolizes the conversions in the following manner. Assume in the first place that fenchyl alcohol loses water in such a way as to form a trimethylene ring within the molecule. The resulting compound may be written in three different ways which are structurally identical:



Now if hydrochloric acid be added on to the molecule in such a way as to break the bond between the carbon atoms numbered 2 and 6, fenchyl chloride will be formed. If, however, the trimethylene ring breaks between the atoms 1 and 6 and rearrangement into a double bond takes place instead of reformation of the trimethylene grouping, then either α- or β-fenchene may be produced.

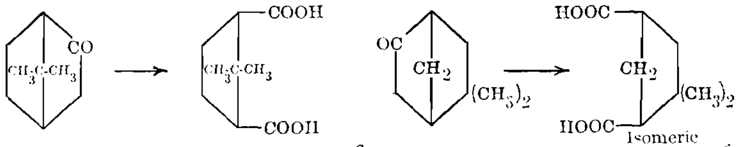


α-Fenchene



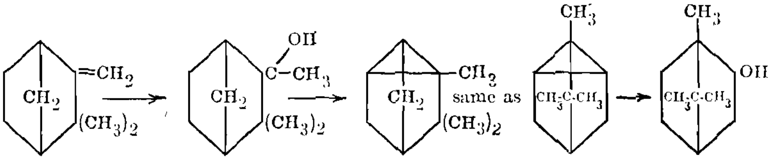
β-Fenchene

The production of apocamphoric acid from α-fenchene and the oxidation of β-fenchene to an isomeric apocamphoric acid are thus symbolized by Collie:



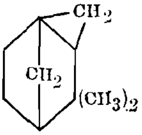
α Fenchocamphorone Apocamphoric Acid β fenchocamphorone Isomeric Apocamphoric Acid

The change of camphene into bornyl alcohol may be accounted for thus:



Camphene Bornyl Alcohol

It should be noted that on Collie's view camphene and the two fenchenes may all be tautomeric forms of a fourth structure which contains a trimethylene grouping.



CHAPTER IX

THE OLEFINIC TERPENES

A.—Introduction

.AVING now described the most important cyclic terpenes, e must next examine the olefinic substances which are often ıcluded in the terpene group. It might seem more logical to eal with the open-chain compounds first, and the cyclic ones .ter; but as we should in that case have had to assume the constitution of certain cyclic terpenes which are closely connected with the olefinic ones, the present method of arrangement is more convenient.

Those unsaturated open-chain substances which are found in ethereal oils, and which, in many cases, can be transformed into cyclic terpenes, are termed olefinic terpenes, or terpenogens. They occur as hydrocarbons, aldehydes, or alcohols, and are derived from hydrocarbons of the formula C_5H_8. In many cases the odour of ethereal oils is very largely due to the olefinic terpenes contained in them.

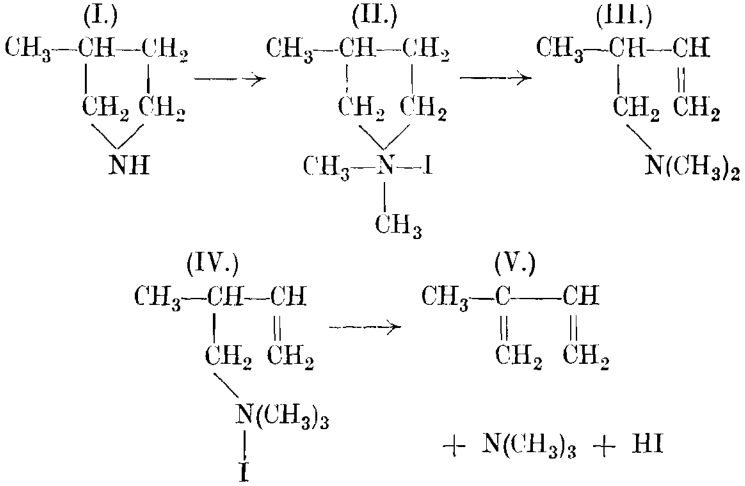
The chemical importance of the olefinic terpenes lies in the fact that from them some of the more complicated terpene derivatives can be found by means of very simple reactions; but they are of interest also from the commercial point of view as forming the basis of many natural and artificial perfumes.

B.—Isoprene

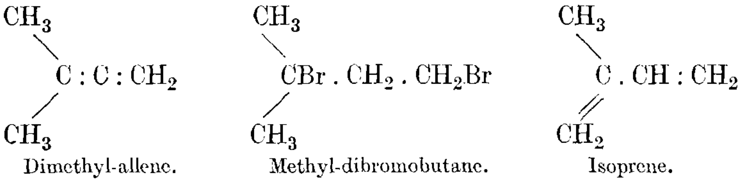
Isoprene is the simplest of all the olefinic terpenes; it contains two double bonds, and has the composition C_5H_8. Its synthesis has been carried out by Euler,[1] and also by Ipatjew,[2] in the one case starting from methyl-pyrrolidine, and in the

[1] Euler, *J. pr. Chem.*, 1898, **57**, 132. [2] Ipatjew, *ibid.*, 1897, **55**, 4.

other from dimethyl-allene. In the first case, the methyl-pyrrolidine (I.) is allowed to interact with methyl iodide with the formation of dimethyl-methylpyrrolidinium iodide (II.). This substance is then decomposed with potash, whereby the ring is broken and *des*-dimethyl-methylpyrrolidine (III.) is produced. The addition of methyl iodide and decomposition of the product (IV.) with potash gives trimethylamine and the required isoprene (V.)—



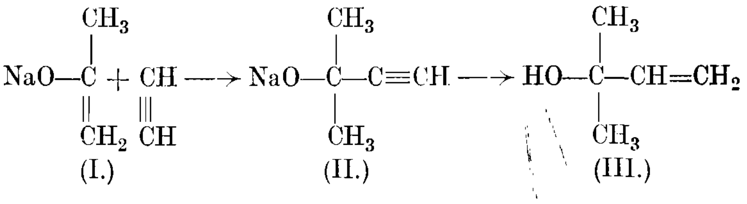
The synthesis from dimethyl-allene is much simpler. Two molecules of hydrobromic acid are added on, forming 2-methyl-2, 4-dibromobutane, from which hydrobromic acid is again split off by means of alcoholic potash—



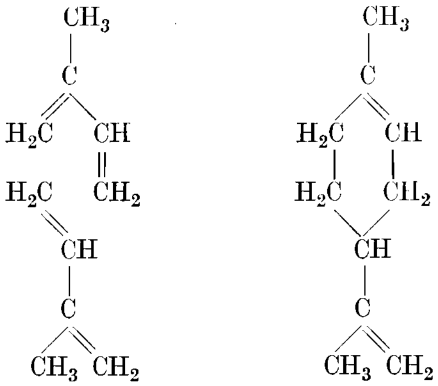
A neat isoprene synthesis has been devised [1] which starts from acetone. On treatment with sodamide, acetone yields a sodium derivative (I.), which is attacked by acetylene to form

[1] Bayer and Co., D.R.P. 280226, 286920, 288271.

(II.). Reduction of this gives rise to (III.), whence isoprene is obtained by removal of one molecule of water.



Isoprene is produced by the dry distillation of indiarubber and by the decomposition of turpentine oil at a dull red heat. Concentrated hydrochloric acid converts it into a polymer which has all the physical properties of indiarubber, and the same change takes place on long standing or with traces of acids in sunlight. When heated to 300° C., isoprene is polymerized to a di-isoprene,[1] which seems to be identical with dipentene :



In a somewhat similar manner isoprene might be supposed to give a sesquiterpene in which three isoprene molecules would coalesce to form a compound of the composition $C_{15}H_{24}$. In any probable reaction of this type, it is worth noting, at least one unsaturated chain will be left untouched and ready to react with further molecules if the proper conditions are obtained; and it is doubtless to this side chain that we owe the more complex polymer which resembles indiarubber.

[1] Tilden, *J.*, 1884, **45**, 410; Bouchardat, *Compt. rend.*, 1875, **80**, 1446; 1878, **87**, 654; 1879, **89**, 361, 1117.

C.—Citronellal

We must now pass to the consideration of a substance rather more complicated than isoprene—the compound citronellal, which was discovered by Dodge [1] in citronella oil. Citronellal is an aldehyde, for on reduction it gives the alcohol citronellol, and on oxidation it forms citronellic acid. Since it is optically active it must contain an asymmetric carbon atom.

Tiemann and Schmidt,[2] oxidizing it in *aqueous* solution, obtained as products acetone and β-methyl-adipic acid, from which they concluded very naturally that citronellal had the constitution :

$$(CH_3)_2C = CH\,.\,CH_2\,.\,CH_2\,.\,CH(CH_3)\,.\,CH_2\,.\,CHO$$

$$\downarrow$$

$$(CH_3)_2CO + \underset{\displaystyle COOH}{\underset{|}{CH_2}}\,.\,CH_2\,.\,CH(CH_3)\,.\,CH_2\,.\,COOH$$

The reason for placing the methyl group in this position will be seen later when we deal with the production of pulegone from this body.

This constitution, however, is not in agreement with the work of Harries and Schauwecker,[3] who approached the matter from a slightly different standpoint. Instead of oxidizing citronellal itself, they prepared its dimethyl-acetal and replaced the aqueous solution of Schmidt and Tiemann by an acetone one. Under these circumstances they found that the oxidation product with potassium permanganate was the acetal of a dihydroxy-dihydrocitronellal, which, on further oxidation with chromic acid, could be converted into a keto-aldehyde. This shows that the double bond must lie at the extreme end of the chain, so that citronellal would have the constitution—

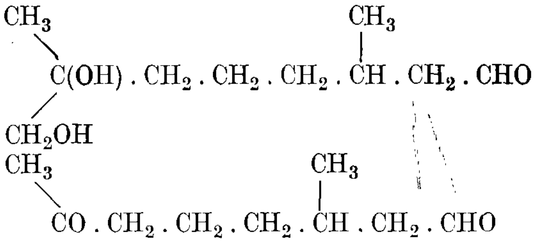
$$\begin{array}{l}CH_3\\ \quad\diagdown\\ \qquad C\,.\,CH_2\,.\,CH_2\,.\,CH_2\,.\,\overset{\displaystyle CH_3}{\overset{|}{CH}}\,.\,CH_2\,.\,CHO\\ \quad/\!\!/\\ CH_2\end{array}$$

[1] Dodge, *Am. Chem. J.*, 1889, **11**, 456.

[2] Tiemann and Schmidt, *Ber.*, 1896, **29**, 903 ; 1897, **30**, 22, 33.

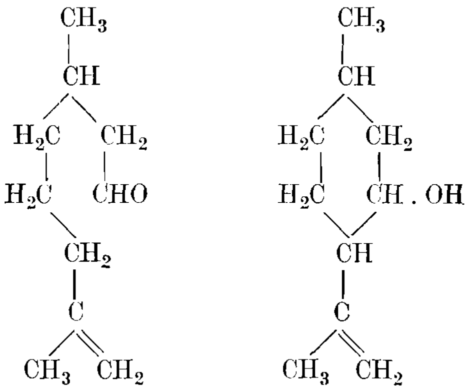
[3] Harries and Schauwecker, *Ber.*, 1901, **34**, 1498, 2981 ; see also Harries and Himmelmann, *Ber.*, 1908, **41**, 2187 ; Harries, *Annalen*, 1915, **410**, 8 ; Rupe, *ibid.*, 1914, **402**, 150.

On this view the dihydroxy-compound and the keto-aldehyde would be—



The results obtained by Tiemann and Schmidt would be explained by supposing that under the influence of the aqueous oxidizing agent the position of the double bond was changed from the ultimate to the penultimate pair of carbon atoms in the chain.

So far we have not proved the position of the methyl group, but we shall now give some evidence bearing upon the point. When citronellal is allowed to stand by itself for a considerable time it is converted into the isomeric substance isopulegol.[1] The same change is brought about more rapidly by heating citronellal with acetic anhydride[2] to 180° C. The change may be represented in the following manner :—

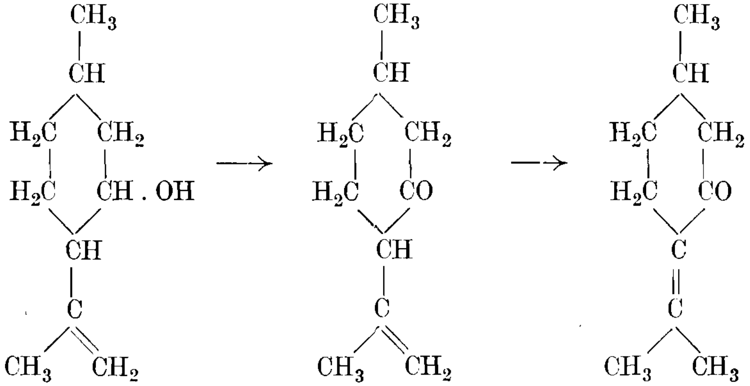


Citronellal. *Isopulegol.*

The proof of the constitution of isopulegol depends upon its conversion into pulegone. When it is oxidized it yields the

[1] Labbe, *Bull. soc. chim.*, 1899, [iii.], **21**, 1023.
[2] Tiemann and Schmidt, *Ber.*, 1896, **29**, 913 ; **30**, 27.

ketone isopulegone, which is converted into pulegone by the wandering of the double bond :



Isopulegol. Isopulegone. Pulegone.

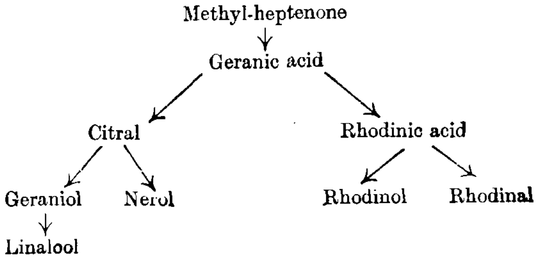
From this it is evident that the methyl group in citronellal must be in the position which we attributed to it ; as otherwise the isopropylene group would not come into the 1, 4-position with it in the pulegone formed from citronellal.

We may postpone the consideration of the alcohol citronellol and of citronellic acid until later, as they are closely connected with some members of the class of compounds with which we are about to deal in the next section.

D.—The Citral Group

1. *General*

The group of olefinic terpenes, of which citral is the most important member, can all be derived from the unsaturated ketone methyl-heptenone. It will perhaps be best, before entering upon a detailed consideration of the group, to give a small table showing the relations between the different members :—

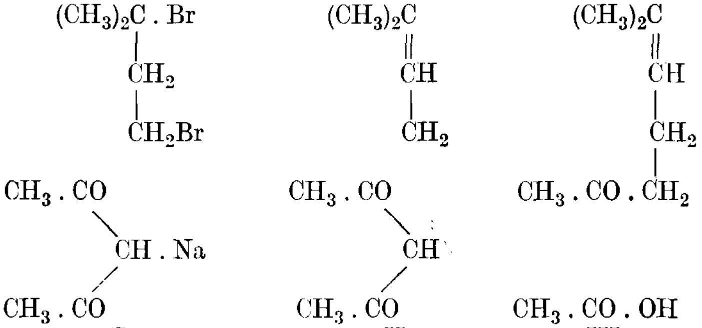


The various changes by which the several substances are obtained must now be described.

2. *Methyl-heptenone*

As can be seen from the foregoing table, the substance from which all the other members of the citral group are built up is the ketone methyl-heptenone. This compound has already been encountered among the decomposition products of cineolic acid, but in that place its constitution was not discussed.

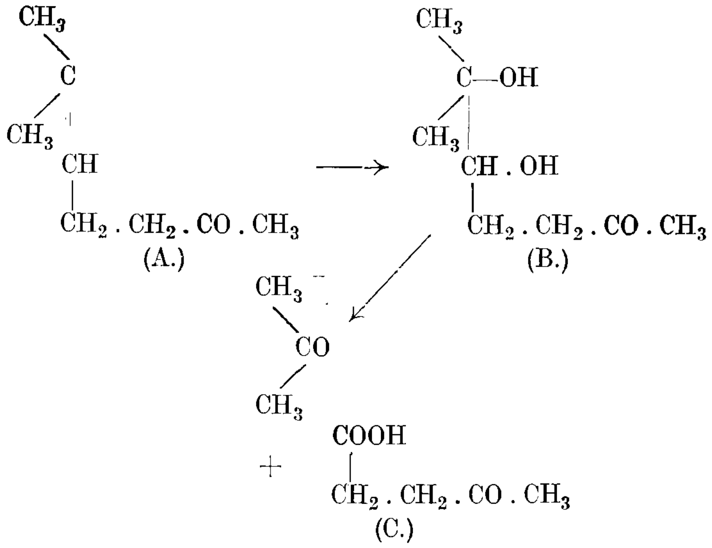
Methyl-heptenone has been synthesized in different ways by Barbier and Bouveault,[1] Verley,[2] Tiemann,[3] Leser,[4] and Ipatjew.[5] Only one synthesis need be given here: that of Barbier and Bouveault. In the first place, 2-methyl-2, 4-dibromobutane was condensed with the sodium derivative of acetylacetone. This gave the unsaturated diketone (II.), which can be broken down by strong alkali into acetic and methyl-heptenone (III.):



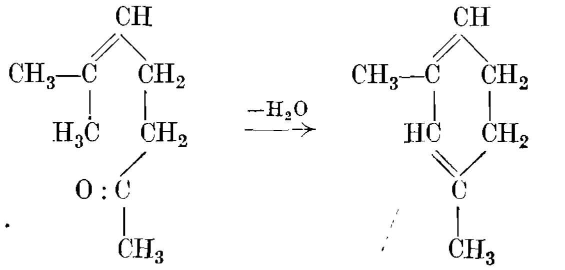
(I.) (II.) (III.)

This establishes the constitution of the substance, but if further proof were required it is to be found in the behaviour of methyl-heptenone (A) on oxidation. The first product (B) is a dihydroxy-ketone, which, on further oxidation, breaks down into acetone and lævulinic acid (C):

[1] Barbier and Bouveault, *Compt. rend.*, 1896, **122,** 393.
[2] Verley, *Bull. soc. chim.*, 1897, [iii.], **17,** 180.
[3] Tiemann, *Ber.*, 1898, **31,** 824.
[4] Leser, *Bull. soc. chim.*, 1897, [iii.], **17,** 180.
[5] Ipatjew, *Ber.*, 1901, **34,** 594.



In itself, methyl-heptenone is of no great importance, and we may confine ourselves to one of the reactions which it undergoes. When shaken with 75 per cent. sulphuric acid it loses a molecule of water and is converted into dihydro-*m*-xylene :



Methyl-heptenone. Dihydro-*m*-xylene.

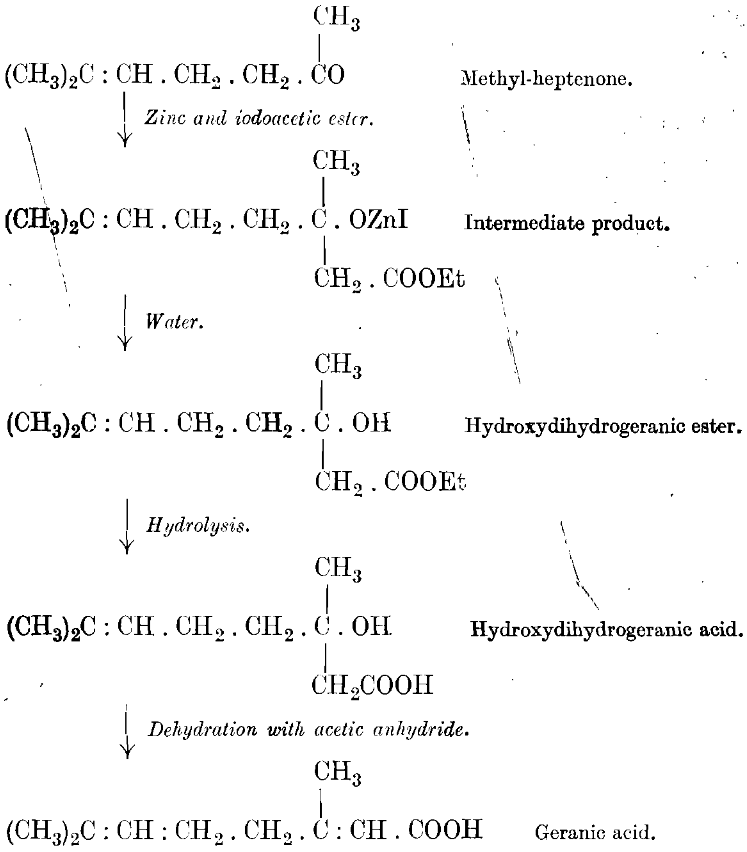
3. *Geranic Acid*

Following upon their synthesis of methyl-heptenone, Barbier and Bouveault [1] were enabled to synthesize geranic acid by means of a simple series of reactions. By the action

[1] Barbier and Bouveault, *Compt. rend.*, 1896, **122**, 398 ; see also Tiemann, *Ber.*, 1898, **31**, 325.

of zinc and iodo-acetic ester upon methyl-heptenone they prepared a hydroxy-acid, which, on boiling with acetic anhydride, broke down into geranic acid.

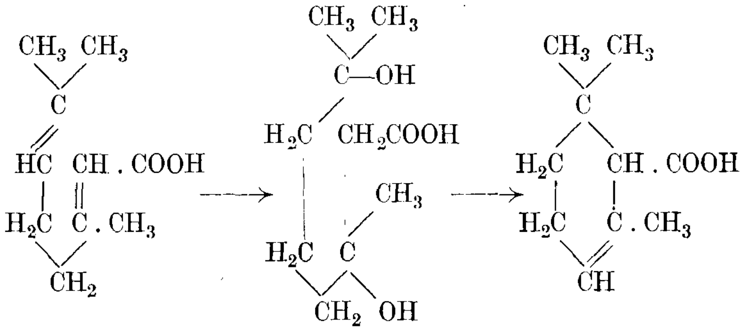
The formulæ below indicate the course of the synthesis :



Like methyl-heptenone, geranic acid is of very little importance in itself. The only reaction which specially concerns us is its condensation to α-cyclogeranic acid,[1] which, like the corresponding condensation of methyl-heptenone, takes place under the influence of 70 per cent. sulphuric acid. In order to explain the geranic acid change, it is necessary to assume

[1] Tiemann and Semmler, *Ber.*, 1893, **26**, 2726 ; Tiemann and Schmidt, *ibid.*, 1898, **31**, 881 ; Tiemann and Tigges, *ibid.*, 1900, **33**, 3713 ; Barbier and Bouveault, *Bull. soc. chim.*, 1896, [iii.], **15**, 1002.

the formation and decomposition of an intermediate product which has not yet been isolated :

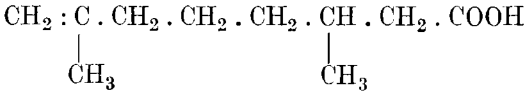


Geranic acid. Hypothetical intermediate product. α-Cyclogeranic acid.

As the table shows, geranic acid gives rise to two series of compounds : on the one hand, by reduction, rhodinic acid and its derivatives are prepared ; while on the other hand, the aldehyde citral can be obtained, from which in turn several substances may be formed. In the first place, the smaller group, rhodinic acid and its allied compounds will be described.

4. *Rhodinic Acid, Rhodinol, and Rhodinal*

When the ethyl ester of geranic acid is reduced by means of sodium and amyl alcohol it is converted into inactive rhodinic acid.[1] The active, lævo-rotatory form of this acid has been obtained from the active alcohol rhodinol. These two acids are isomeric with citronellic acid, which is obtained by the oxidation of the aldehyde citronellal, and it has been suggested that citronellic acid is the dextro-form of rhodinic acid. On the other hand, from the constitution of citronellal, it might be expected that citronellic acid obtained from it by oxidation would have the formula (I.), while rhodinic acid from geranic acid should have the formula (II.).



Citronellic acid.

(I.)

[1] Tiemann, *Ber.*, 1898, **31**, 2901.

$$(CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2 \,.\, \underset{\displaystyle |\atop \displaystyle CH_3}{CH} \,.\, CH_2 \,.\, COOH$$

Rhodinic acid.

(II.)

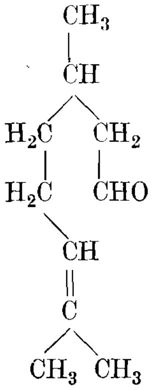
The literature of the subject is somewhat contradictory, and it does not seem necessary to go into the question in detail here.

When the ester of rhodinic acid is reduced by means of sodium and absolute alcohol it yields the corresponding alcohol [1] rhodinol:

$$(CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2 \,.\, \underset{\displaystyle |\atop \displaystyle CH_3}{CH} \,.\, CH_2 \,.\, CH_2OH$$

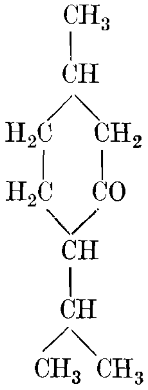
which is isomeric with citronellol. Here, again, the literature is contradictory, and it seems impossible to decide whether the two compounds are stereo-isomers or different in structure.

Rhodinal,[2] the aldehyde corresponding to the alcohol rhodinol, is obtained by distilling together calcium formate and the calcium salt of rhodinic acid. Barbier and Bouveault regard it as having the structure (I.), because of its conversion into menthone. Citronellal, with which it is isomeric, when submitted to the action of acetic anhydride, is changed into isopulegol, as we have already described. On the other hand, rhodinal when treated in the same way yields menthone:



Rhodinal.

(I.)



Menthone.

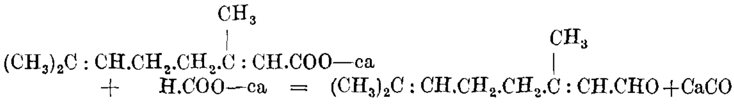
(II.)

[1] Bouveault and Gourmand, *Compt. rend.*, 1904, **138**, 1699.

[2] Tiemann, *Ber.*, 1898, **31**, 2902.

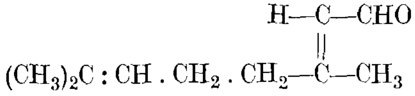
5. *Citral*

By distilling together the calcium salts of formic and geranic acids, the aldehyde citral is obtained.[1] Since this is a general reaction, the constitution of citral would probably be that shown in the equation below :

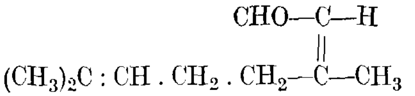


In support of this formula there is further evidence to be found in the decomposition of citral into acetaldehyde and methyl-heptenone, which takes place when the substance is warmed with a solution of sodium carbonate.

Citral, therefore, represents rhodinal or citronellal from which two hydrogen atoms have been withdrawn ; and differs from them further in that it contains no asymmetric carbon atom. But though it loses this possibility of isomerism, it retains another, for it has been found to occur in two geometrically isomeric forms :[2]



Citral *a*.



Citral *b*.

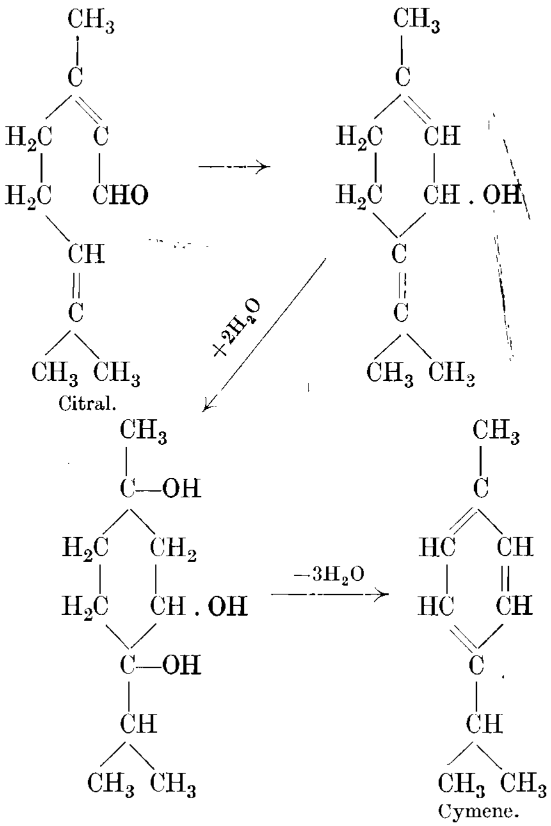
These have been shown by Harries and Himmelmann to be structurally identical ; and the relative configurations have been inferred from the relations of the two compounds to geraniol and nerol, which will be described later.

Like the other olefinic terpenes, citral can be converted into cyclic substances with great ease. When it is boiled for a long time with glacial acetic it is changed into cymene :[3]

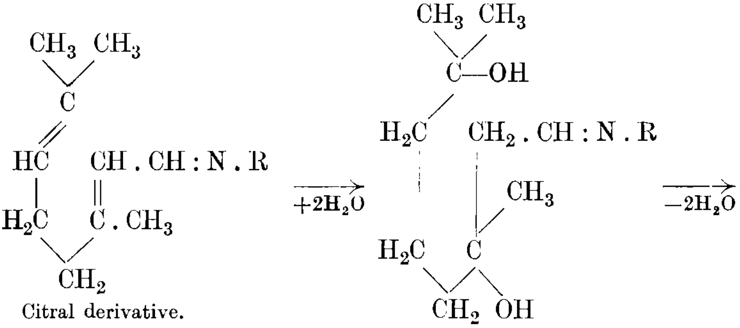
[1] Tiemann, *Ber.*, 1898, **31**, 827, 2899.

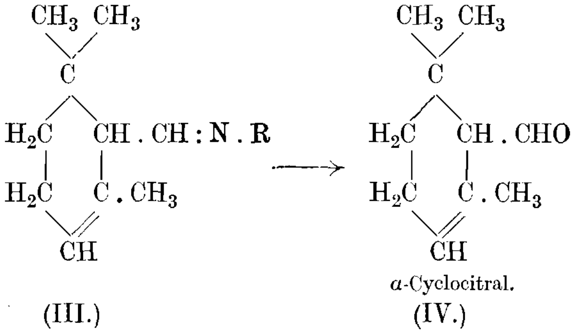
[2] Tiemann, *Ber.*, 1899, **32**, 115 ; 1900, **33**, 877 ; Bouveault, *Bull. soc. chim.*, 1899, [iii.], **21**, 419, 423 ; Barbier, *ibid.*, 635 ; Kerschbaum, *Ber.*, 1900, **33**, 886 ; Zeitschel, *Ber.*, 1906, **39**, 1783 ; Harries and Himmelmann, *Ber.*, 1907, **40**, 2823.

[3] Tiemann and Semmler, *Ber.*, 1895, **28**, 2134.



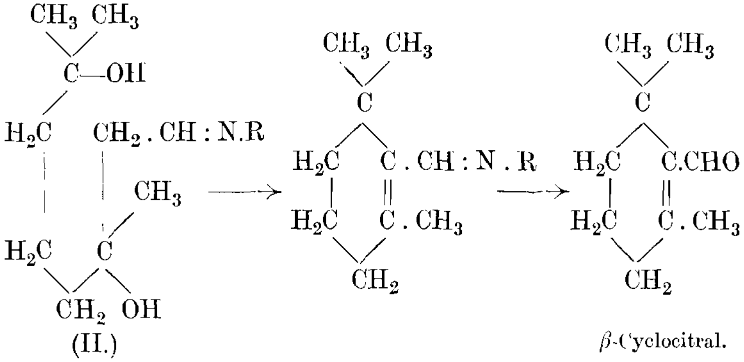
A second condensation of citral takes place when the aldehyde group is so treated that it takes no part in the action. For instance, if citral be condensed with a primary amine, we obtain a cyclo-citral by a simple wandering of bonds and ring-formation :





The same result may be obtained by condensing citral with cyan-acetic ester instead of an amine. In each case, the amine or cyan-ester can be split off after the condensation to cyclo-citral has taken place.

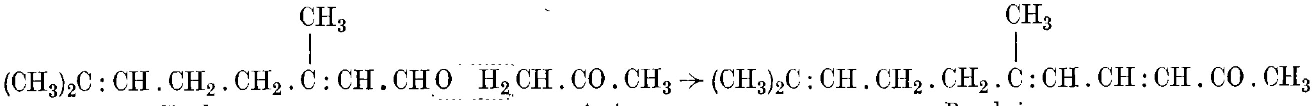
Cyclo-citral occurs in two isomeric forms,[1] the formation of either being dependent upon the manner in which water is eliminated from the molecule of an intermediate hydration product (II.). The formation of β-cyclocitral takes place as shown below :



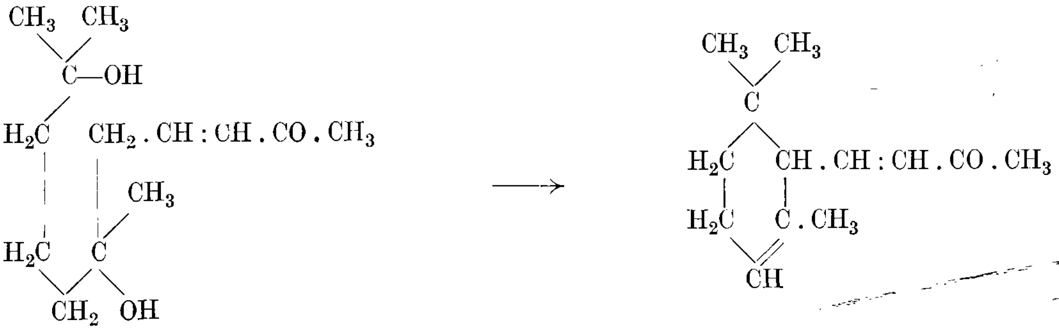
The practical interest of citral lies in the fact that when it is condensed with acetone by means of baryta, it yields a substance, pseudo-ionone, which, by the action of sulphuric acid, is changed into ionone,[2] the basis of artificial violet perfume.

[1] Tiemann, *Ber.*, 1900, **33**, 3719.

[2] Tiemann and Krüger, *Ber.*, 1893, **26**, 2691 ; Tiemann, *ibid.*, 1898, **31**, 808, 867, 1736, 2313 ; 1899, **32**, 827 ; Tiemann and Schmidt, *ibid.*, 1900, **33**, 3703.

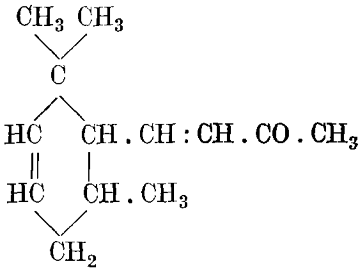


Citral. Acetone. Pseudo-ionone.



Pseudo-ionone hydration product. Ionone.

This body differs from the natural substance irone (to which the odour of violets is due) only in the position of a double bond :



Irone.

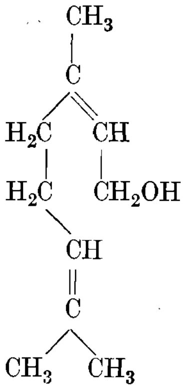
6. *Geraniol, Nerol, and Linalool*

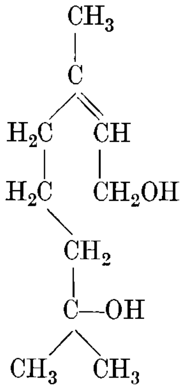
If citral be reduced with sodium amalgam in an alcoholic solution weakly acidified with acetic acid, a mixture of two isomeric alcohols, geraniol and nerol, is obtained. These two bodies, on oxidation, regenerate citral, and on this ground, as well as on account of other reactions common to both, it is assumed that they are structurally identical but stereoisomeric substances of the formula—

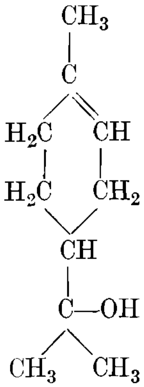
$$(CH_3)_2C : CH \,.\, CH_2 \,.\, CH_2 \,.\, \underset{}{\overset{\overset{\displaystyle CH_3}{|}}{C}} : CH \,.\, CH_2OH$$

Proof of the correctness of this formula is afforded by the fact that when geraniol is heated with water to 150° C. it gives ethyl alcohol and methyl-heptenone ; while on oxidation it gives acetone, lævulinic acid, and oxalic acid.

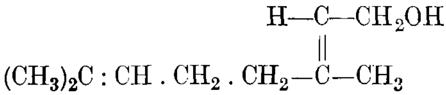
By the action of acetic acid, to which 1 or 2 per cent. of sulphuric acid has been added, both nerol and geraniol give terpineol :

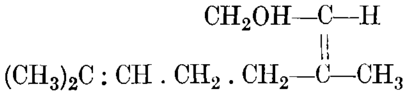

Geraniol.


Hypothetical glycol.


Terpineol.

Now, this reaction takes place nine times faster with nerol than with geraniol; and if the two bodies are geometrical isomers, this difference allows a conclusion to be drawn with regard to their configurations.[1] A comparison of the two formulæ below will suffice to show that in (I.) the groups which unite to form the terpineol ring are further apart in space than they are in (II.). The ring-formation will therefore occur more easily in the case of (II.) than in that of (I.). Hence the first formula must be allotted to geraniol and the second to nerol:

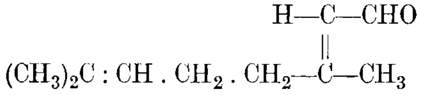

Geraniol.
(I.)


Nerol.
(II.)

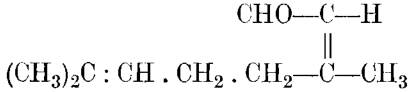
We are now able to deal with the space formulæ of the two citrals. The oxidation of geraniol gives a mixture of citral *a* and citral *b*, in which citral *a* predominates; while with nerol the proportions are reversed, more citral *b* being formed. From

[1] Zeitschel, *Ber.*, 1906, **39**, 1780.

this may be inferred that citral *a* has the same configuration as geraniol, while citral *b* has its groups arranged as in nerol—



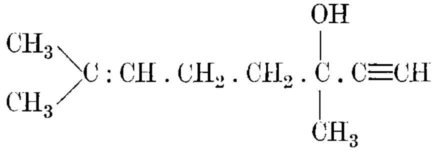
Citral *a* (Geranial).



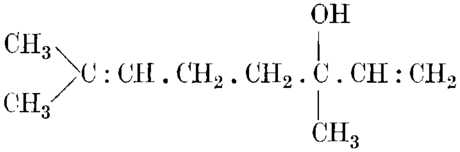
Citral *b* (Neral).

Both geraniol and nerol are found in nature as inactive substances, which agrees with the formulæ which we have ascribed to them above. The isomeric compound, linalool, however, occurs in both dextro- and lævo-rotatory forms, and must therefore contain an asymmetric carbon atom.

This is confirmed by the synthesis of linalool, which has been carried out in the following manner.[1] An ethereal solution of methyl-heptenone was treated with sodamide, and acetylene was then passed through the liquid. In this way dehydro-linalool was formed :



Reduction of this was accomplished by adding sodium and drops of water to the oily material, and *dl*-linalool was formed. This establishes for linalool the formula :

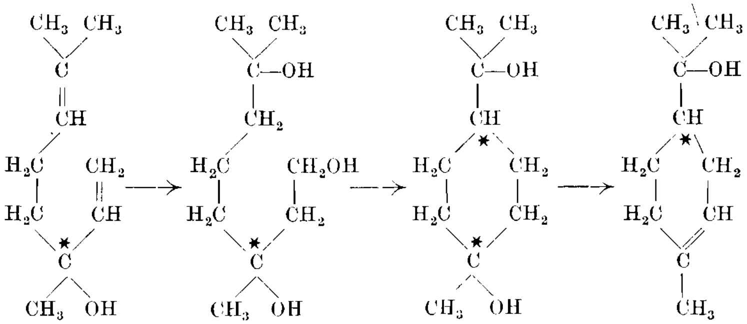


The inactive form of linalool is convertible into both geraniol and nerol by the action of acetic anhydride. A comparison of the formulæ given above for the three compounds will show that by the addition of water to each of them a glycol of the formula :

[1] Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, 2, 182.

$$(CH_3)_2C : CH . CH_2 . CH_2 . \overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}} . CH_2 . CH_2OH$$

can be produced. This formation of a common hydration product suffices to explain the interconvertibility of the three isomers; but there is one further point which seems to suggest that linalool formula is a peculiar substance. When lævo-linalool is treated with acetic anhydride, terpineol is formed along with nerol and geraniol; and this terpineol is found to be dextrorotatory. But on comparing the formulæ of terpineol and linalool, it is found that the asymmetric carbon atom of linalool does not correspond to that in terpineol; in fact, the atom which in linalool was asymmetric is now not asymmetric, while a new asymmetric carbon atom has come into being. In the formulæ below, the asymmetric carbon atoms are indicated by asterisks. How optical activity can persist through such a change as this appears difficult to understand, unless we assume that it is a case of asymmetric synthesis.



l-Linalool. Intermediate products. *d*-Terpineol.

This terminates the present survey of the terpene class. In conclusion, a table may be appended to this chapter to show some of the possible conversions of monocyclic, dicyclic, and olefinic terpenes into each other, and also into members of the benzene series.

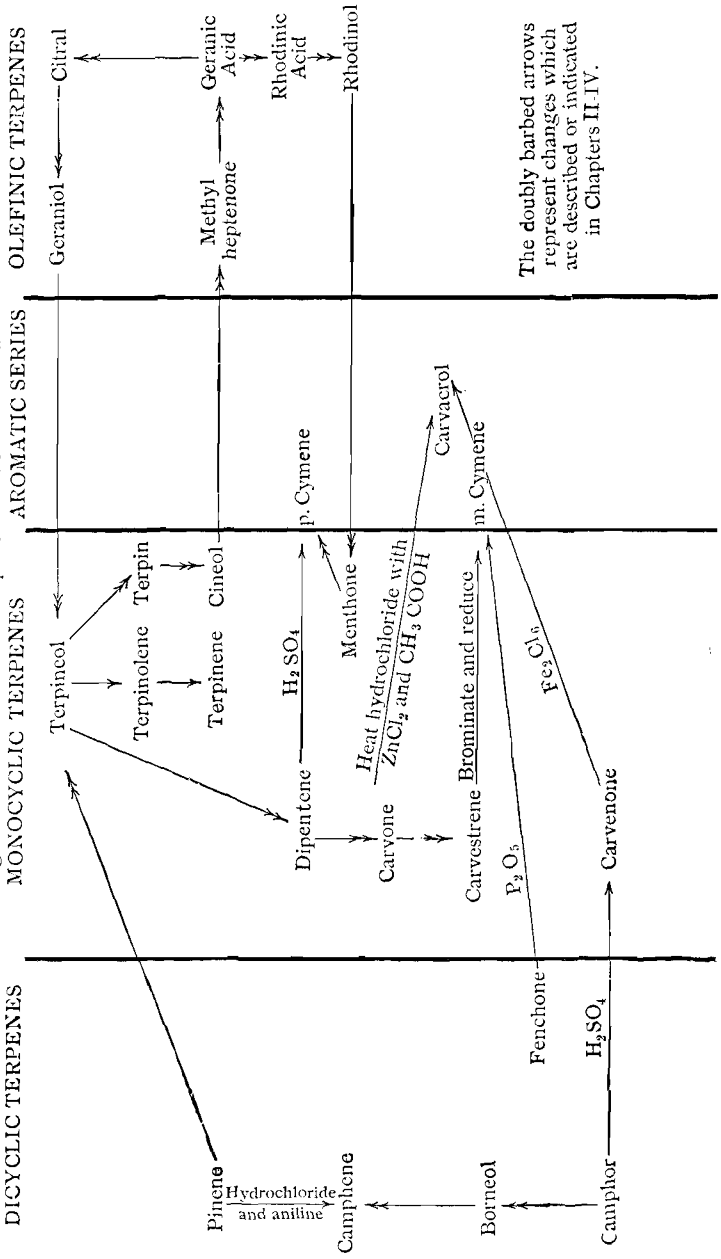


Table showing some Relations between Terpenes & Benzene Derivatives.

CHAPTER X

THE PYRROL, PYRIDINE, AND TROPINE ALKALOIDS

A.—General

Although the word "alkaloid" is one of the best-known in chemical terminology, an exact definition of its meaning is by no means simple. For present purposes, a general idea of alkaloidal character is more important than an academic definition; and the following description will suffice here.

The alkaloids are naturally-occurring nitrogen compounds, which possess certain specific physiological actions upon animal organisms. Thus atropine has a mydriatic effect and is used for expanding the pupil of the eye; quinine is employed as a febrifuge to reduce temperature during fever; strychnine produces the muscular effects noticed in cases of strychnine poisoning; and cocaine acts as a local anæsthetic. In the majority of alkaloids, but not in all, the nitrogen atom is a member of a ring-system such as pyrrol, pyridine, or quinoline; and even in cases where it is part of an open chain it is either secondary or tertiary in character. In consequence, the majority of alkaloids have basic characteristics; but this is not an invariable rule, since some of the purine group are acidic in their nature.

On examination of the more familiar alkaloids it is found that they are built up on the basis of the pyridine ring, just as the aromatic compounds are founded on the benzene nucleus; and as among aromatic types a benzene ring is sometimes found to be condensed with other cyclic chains, so in the pyridine alkaloids there are compounds wherein the pyridine ring is overlaid with others, yielding derivatives of quinoline or iso-quinoline.

Since in most cases alkaloids occur as salts, they are obtained from the actual plant tissues by the action of alkali, which liberates the basic part of the molecule. If this be volatile in steam, the alkaloid is obtained in that way; but if it be not thus volatile it is extracted from the tissues by treating them with acids, which dissolve the alkaloids, forming solutions of their salts, from which the free alkaloid is obtained by the action of alkali. Final purification is carried out by crystallization of the alkaloid or of its salts. When extraction is carried out on a small scale, chloroform is often used to remove alkaloids from the tissues in which they occur.

The majority of alkaloids are solid substances, but one or two are liquids which can be distilled without decomposition. Nearly all of them have powerful actions upon the animal organism; but owing to our ignorance of the relation between chemical constitution and physiological action, not much can be said on the subject. In most cases alkaloids are found to possess lævo-rotation, and it is very seldom that both optically active forms are found in nature.

B.—Methods employed in the Determination of Alkaloid Constitutions

After the composition and molecular weight of an alkaloid have been determined by the usual methods, the next step is to ascertain the manner in which the atoms are linked together within the alkaloidal molecule; and at this point it seems advisable to give a brief account of some of the more important reactions which are employed to solve the problem.

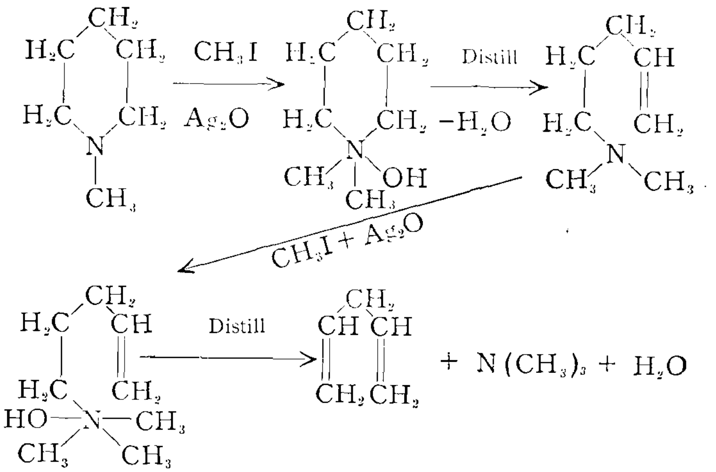
In the first place, since many alkaloids are known to be esters, it is usual to employ some hydrolytic method in order to see whether or not the alkaloid molecule can be decomposed into some simpler grouping. To this end the alkaloid may be heated with water, acids, or alkalis until it is decomposed into its component acid and base. This method, while breaking up any salt or ester, does not, except in a few cases, result in any further destruction of the body; so that from the constitutions of the two halves we are able to deduce the constitution of the parent substance.

This method of decomposition, however, may not go far enough, and it is usually seconded by a more violent action. For instance, the alkaloid may be fused with alkali, distilled with zinc dust, heated with bromine or phosphoric acid. When reagents such as these are employed, the less durable part of the molecule is usually shattered ; and in the reaction-product we find some stable nucleus such as pyridine, quinoline, or isoquinoline, from which the whole alkaloid is derived.

Again, many alkaloids exist in the form of methyl ethers. These can be broken up by boiling with hydriodic acid (Zeisel's method) ; and by passing the methyl iodide thus formed into silver nitrate solution the number of methyl radicles split off by the hydriodic acid may be estimated, and thus the number of methoxyl groups in the alkaloid can be ascertained.

When the alkaloid contains an oxygen atom, it is of importance to determine whether this occurs in a carbonyl, carboxyl, hydroxyl, or ether group. The first is determined in the usual way by the action of phenylhydrazine or hydroxylamine ; the hydroxyl group can usually be detected by acylating it or by the action of dehydrating agents, which split off water and leave an unsaturated substance ; while if the alkaloid is an alkyl ether it can often be decomposed by Zeisel's method. If the carboxyl group occurs in the alkaloid under examination, there is not much difficulty in detecting its presence.

All alkaloids contain nitrogen, but it is necessary to discover in what way this nitrogen is linked with the rest of the molecule. Herzig and Meyer have devised a method of determination for methyl-imino groups which is very useful in this branch of research. The hydriodides of bases in which a methyl group is attached to nitrogen, when heated to about 300° C., split off methyl iodide, which can be estimated with silver nitrate just as in the case of the methoxyl group. A somewhat similar decomposition results in the reaction which is usually termed "exhaustive methylation." Here, by the action of methyl iodide and silver oxide, assisted by dry distillation, a cyclic nitrogen compound may be made to lose its nitrogen atom with but little alteration in the rest of the molecule. The formulæ will make the process clear without further explanation :—



The final stages in determining the constitution of any alkaloid are usually those in which the oxidation products of the substance are studied. All the agents employed are well-known, so it is unnecessary to describe their actions. The most useful are potassium permanganate, hydrogen peroxide, dilute nitric acid and chromic acid.

C.—The Pyridine Group

1. *Coniine*

The first alkaloid with which we shall deal is the substance coniine, which deserves the foremost place on two grounds: it is the simplest member of the alkaloid class, and it is the first alkaloid which has been completely synthesized from the elements. The complete synthesis will be given in the case of this substance, as it is of historical interest.

By heating together carbon and sulphur we can produce carbon disulphide, which, by the action of chlorine, is converted into carbon tetrachloride. By heat, this can be changed into perchlorethylene, $Cl_2.C:C.Cl_2$, and when this is acted on by ozonized air it yields trichloracetic acid. Reduction with potassium amalgam in aqueous solution changes trichloracetic acid into acetic acid. From this, acetone is obtained by

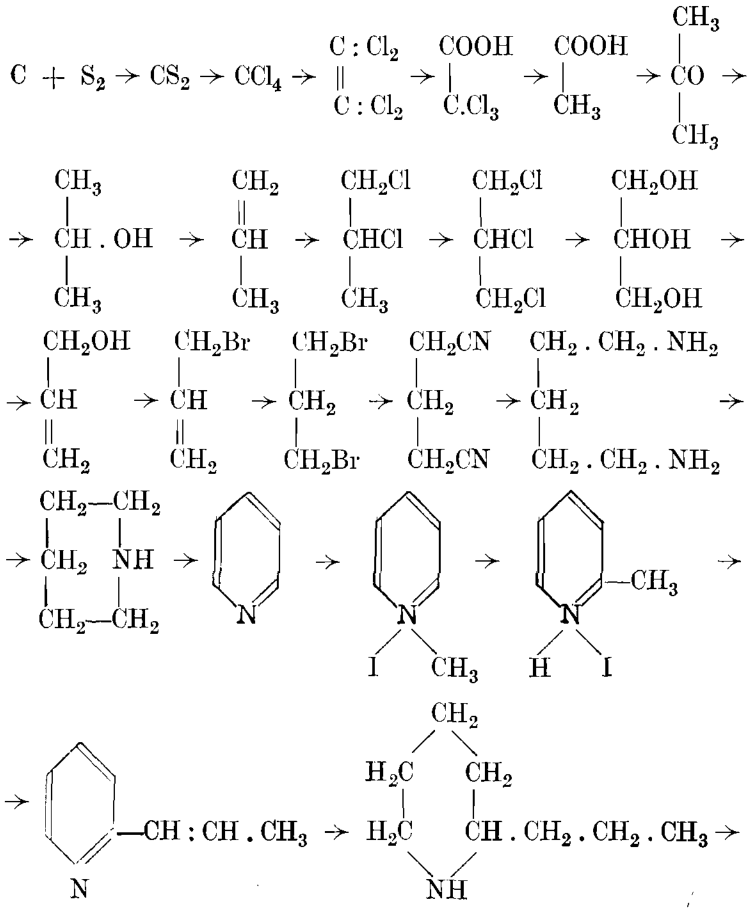
distillation of calcium acetate, and by reducing the acetone so formed we can produce isopropyl alcohol. The action of zinc chloride upon the alcohol gives propylene by dehydration, and propylene chloride can then be obtained by the addition of chlorine. Propylene chloride and iodine chloride together yield trichlorohydrin, from which glycerine is produced by heating the trichloride to 160° with a large excess of water. Glycerine, on dehydration, gives allyl alcohol; and this, in turn, allyl bromide; from which, by the addition of hydrobromic acid, trimethylene bromide is formed. By replacing the bromine atoms by cyanogen groups glutaric nitrile is prepared, and this, by reduction, gives pentamethylene diamine. On dry distillation, the hydrochloride loses ammonium chloride and is converted into piperidine,[1] from which pyridine * can be obtained by oxidation. Pyridine combines with methyl iodide, and when the pyridinium methyl iodide thus produced is heated to about 300° C. it suffers intramolecular change and is converted into the hydriodide of α-picoline. Picoline, when heated to a high temperature with paraldehyde, gives α-propenyl-pyridine, which, on reduction, gives isoconiine.[2] On further heating to 300° C., or boiling with solid potash, this is converted into racemic coniine.[3] To separate the right- and left-handed forms, active tartaric acid is used, since this substance can also be obtained synthetically and its two antipodes can be separated from each other by means of the sodium ammonium salt without the interposition of any naturally occurring optically active substance. The formulæ below give the steps which we have mentioned :

[1] Ladenburg, *Ber.*, 1855, **18**, 3100.

* Pyridine was obtained in a simpler way by Ramsay (*Ber.*, 1877, **10**, 736) by passing a mixture of acetylene and hydrocyanic acid through a heated tube. Since acetylene is produced by a carbon arc in a hydrogen atmosphere, and hydrocyanic acid is formed by sparking a mixture of acetylene and nitrogen, this forms a simpler synthesis from the elements.

[2] Ladenburg, *Ber.*, 1889, **22**, 1403.

[3] Ladenburg, *Ber.*, 1906, **39**, 2486.



→ (*d* + *l*)-Coniine → *d* or *l*-Coniine.

2. *Piperine*

When the alkaloid piperine is boiled with alcoholic potash it is decomposed into piperidine and piperic acid.[1] The constitution of piperidine is established by the Ladenburg synthesis from pentamethylene diamine (which was already mentioned in connection with the synthesis of coniine), as well as by the formation of piperidine from pyridine, by reduction. In order

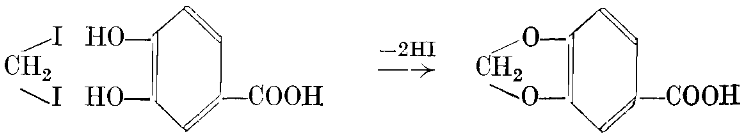
[1] Babo and Keller, *J. pr. Ch.*, 1857, **72**, 53.

to establish the constitution of piperine, therefore, it is only necessary to determine the constitution of piperic acid.

The decomposition of piperine may be expressed in the following way :—

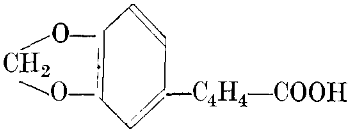
$$\underset{\text{Piperine.}}{C_{17}H_{19}O_3N} + H_2O = \underset{\text{Piperidine.}}{C_5H_{11}N} + \underset{\text{Piperic acid.}}{C_{12}H_{10}O_4}$$

Fittig, by the action of permanganate, oxidized piperic acid to an aldehyde, piperonal,[1] which has the composition $C_7H_5O_2 . CHO$. On further oxidation, piperonal is converted into the corresponding acid, piperonylic acid, $C_7H_5O_2 . COOH$. Now, this substance can be synthesized by the action of methylene iodide upon protocatechuic acid in presence of caustic potash, and therefore it must be the methylene ether of that acid.



Protocatechuic acid. Piperonylic acid.

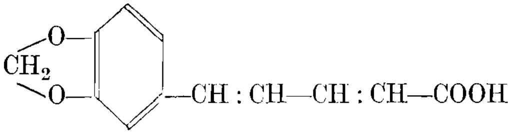
By subtracting the atoms in piperonylic acid from those which make up piperic acid, we find a surplus of four carbon and four hydrogen atoms. This set —C_4H_4— must be so attached to the benzene ring of piperonylic that on oxidation it disappears entirely and does not give rise to a second carboxyl group in the molecule. The only way in which this condition can be fulfilled is by inserting the group —C_4H_4— between the carboxyl group and the benzene ring of piperonylic acid. Piperic acid would thus be expressed by this formula :



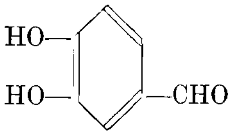
When piperic acid is allowed to react with bromine, it takes up four atoms of the halogen, thus showing that it contains

[1] Fittig and Remsen, *Annalen*, 1871, **159**, 142.

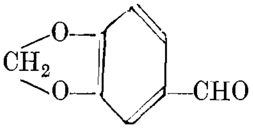
two double bonds. These double bonds must be in the side-chain between the nucleus and the carboxyl group, hence we may ascribe the following formula to piperic acid—



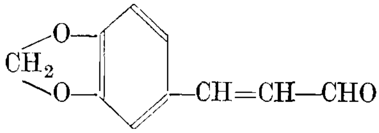
The synthesis of piperic acid has been carried out in the following way. Synthetic protocatechuic aldehyde [1] was converted by methylene iodide and potash into piperonal,[2] which, when warmed with acetaldehyde and very dilute alkali (Claisen's reaction), forms piperonal-acrolein :



Protocatechuic aldehyde.

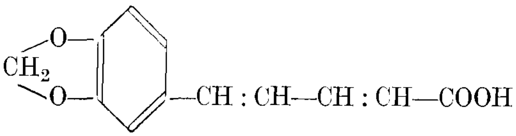


Piperonal.



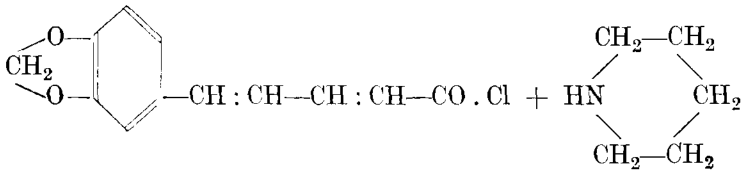
Piperonal-acrolein.

When this acrolein derivative is heated for several hours with sodium acetate and acetic anhydride it condenses with a molecule of acetic acid (Perkin's reaction), and forms piperic acid : [3]

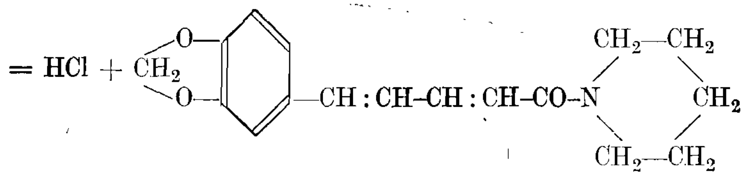


By converting piperic acid into its chloride and heating the latter with piperidine in benzene solution, piperine is formed.[4]

[1] Tiemann and Koppe, *Ber.*, 1881, **14**, 2015.
[2] Wegscheider, *Monatsh*, 1893, **14**, 382.
[3] Ladenburg and Scholtz, *Ber.*, 1894, **27**, 1958.
[4] Rügheimer, *Ber.*, 1882, **15**, 1390; Fittig and Remsen, *Annalen*, 1871, **159**, 142.



Piperic acid chloride. Piperidine.



Piperine.

In this way the alkaloid can be synthesized, its constitution being proved by the synthesis and further certified by the decomposition reactions which have been mentioned.

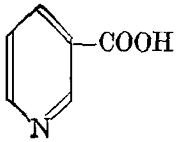
3. *Trigonelline.*

This alkaloid has the composition $C_7H_7NO_2$. It was discovered by Jahns[1] in 1885; and in the following year its constitution was proved by Hantzsch,[2] who obtained it unintentionally in the course of an examination of some derivatives of nicotinic acid.

Hantzsch treated nicotinic acid (I.) with caustic potash and methyl iodide, obtaining the methyl ammonium iodide of nicotinic methyl ester (II.). When this is acted on by silver oxide the iodine atom is exchanged for a hydroxyl group, and the compound (III.) is produced, which at once loses water and is converted into a betaine (IV.). This synthetic body was isomeric with trigonelline, and on comparing the two substances Jahns[3] found them to be identical. Trigonelline is therefore the methyl-betaine of nicotinic acid.

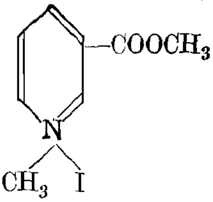
[1] Jahns, *Ber.*, 1885, **18**, 2518.
[2] Hantzsch, *Ber.*, 1886, **19**, 31.
[3] Jahns, *Ber.*, 1887, **20**, 2840.

(I.)



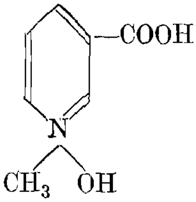
Nicotinic acid.

(II.)



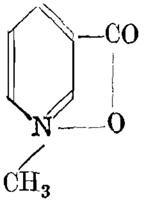
Ester.

(III.)



Hydroxy-acid.

(IV.)



Betaine (Trigonelline).

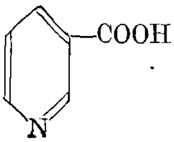
D.—The Pyridine-Pyrrolidine Group.

Nicotine

The alkaloid nicotine stands in a position midway between the pyridine and the pyrrolidine groups; for, as will be shown presently, it contains both a pyridine and a pyrrolidine nucleus. It therefore forms a convenient bridge by which to pass from the consideration of the one class to the other.

Nicotine is a basic substance having the composition $C_{10}H_{14}N_2$. Its constitution has been established by means of the following reactions :—

1. Nitric acid, chromic acid, or potassium permanganate oxidize nicotine [1] to nicotinic acid :



[1] Huber, *Annalen,* 1867, **141**, 271; Weidel, *Annalen,* 1873, **165**, **328**; Laiblin, *Ber.,* 1877, **19**, 2136.

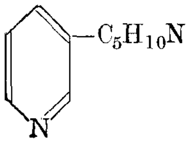
2. By the action of bromine upon nicotine, two derivatives [1] are formed—

    (*a*) Dibromocotinine, $C_{10}H_{10}Br_2N_2O$.

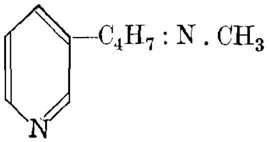
    (*b*) Dibromoticonine, $C_{10}H_8Br_2N_2O_2$.

3. When dibromocotinine is decomposed by bases it gives methylamine, oxalic acid, and a compound C_7H_7NO. By the same treatment dibromoticonine yields methylamine, malonic, and nicotinic acids.
4. Nicotine is a di-tertiary base,[2] giving two isomeric methyl iodide addition products.

From the first reaction it is obvious that nicotine must be *pyridine, with a side-chain in the β-position.*



From the third reaction it is clear that of the two nitrogen atoms in nicotine, one carries a methyl group. This one cannot be the pyridine nitrogen. Further, the second nitrogen atom (which *does* carry the methyl radicle) cannot belong to a pyridine ring. We may thus go a step further, and represent nicotine by the formula :



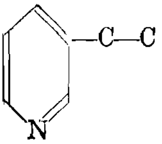
Again, the third reaction shows us that dibromocotinine and dibromoticonine give rise to three carbon chains :

$C—CH_2—C$

Malonic acid chain.

—C . C—

Oxalic acid chain.

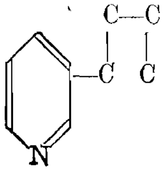


C_7H_7NO chain.

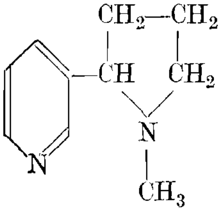
These must be somehow combined in the nicotine molecule, so we may write the nicotine skeleton thus :

[1] Pinner, *Ber.*, 1893, **26**, 292.

[2] Pictet and Genequand, *Ber.*, 1897, **30**, 2117.



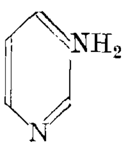
To this we must attach the group: $=N.CH_3$ in some way. From the fourth reaction we deduce that this nitrogen atom is a tertiary one, so that the two isomeric methyl iodide addition products may be explained by the addition of methyl iodide to a different nitrogen atom in each case. But if the group $:N.CH_3$ is to contain a tertiary nitrogen atom, and also to be attached to the nicotine skeleton given above, the only way is to make the nitrogen atom a member of a ring. The constitution of nicotine would then be—



Nicotine.

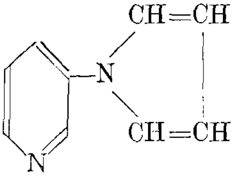
The synthetic preparation of nicotine proved to be a much harder task than was anticipated. The first steps were taken by Pictet and Crépieux,[1] who, by heating β-amino-pyridine (I.) with mucic acid, were able to produce (II.) N-β-pyridyl-pyrrol. Like many other N-alkyl derivatives of pyrrol, this substance when passed through a heated tube undergoes a molecular rearrangement, in the course of which the pyridine group is transferred to the carbon atom next the nitrogen in the pyrrol ring. The compound thus formed is $\alpha\beta$-pyridyl-pyrrol (III.):

(I.)



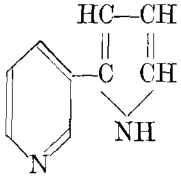
β-amino-pyridine.

(II.)



N-β-pyridyl-pyrrol.

(III.)

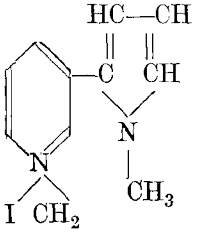


β-pyridyl-α-pyrrol.

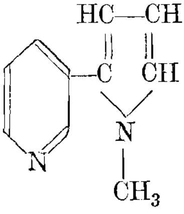
[1] Pictet and Crépieux, *Ber.*, 1895, **28**, 1094.

From this substance Pictet[1] continued the synthesis in the following way. The $\alpha\beta$-pyridyl-pyrrol forms a potassium salt, the imino-hydrogen of the pyrrol group being replaced in the usual way by the metallic atom; and from this salt, by the action of methyl iodide, the methyl derivative of the iodo-methylate (IV.) is obtained. On distillation with lime, this forms the base nicotyrine (V.):

(IV.)



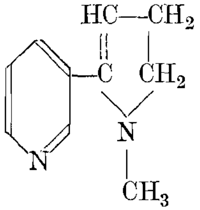
(V.)



Nicotyrine.

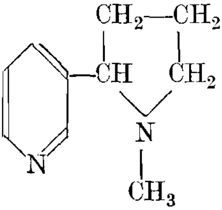
Now, this body cannot be reduced direct to nicotine, for any agent which attacks the pyrrol nucleus will, at the same time, reduce the pyridine ring. The transformation can be carried out in the following way, however. The nicotyrine (V.) is treated with iodine in alkaline solution, by which means a mono-iodine derivative is produced; it in turn is acted on by tin and hydrochloric acid, whereby it is partially reduced, forming dihydro-nicotyrine (VI.). This substance reacts with bromine to form a perbromide, $C_5H_4N . C_5H_8N . Br_4$, which by reduction with tin and hydrochloric acid, yields inactive nicotine (VII.). This racemic base can, like coniine, be resolved into its antipodes by means of tartaric acid; so that in this way the synthesis of lævo-nicotine, corresponding to the natural alkaloid, can be accomplished:

(VI.)



Dihydro-nicotyrine.

(VII.)



Nicotine.

[1] Pictet, *Compt. rend.*, 1903, **137**, 860.

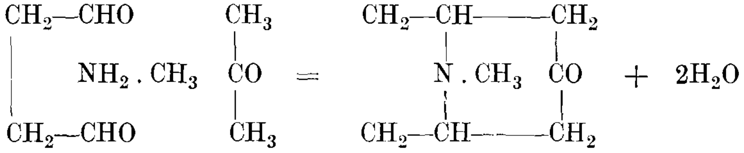
E.—The Tropine Group

1. *Tropinone, Tropine, and ψ-Tropine* *

Hitherto attention has been confined to compounds which contain isolated rings of carbon and nitrogen atoms; but with the tropine series we enter a new class in which we shall have to deal with bridged rings analogous to those of the dicyclic terpenes. The first member of the group is tropinone.

This substance was originally prepared by an extremely round-about method;[1] but a new direct synthesis has been devised by Robinson,[2] so that it is unnecessary to describe the older method, which involved nearly twenty stages.

Succindialdehyde (obtained from succindialdoxime and nitrous fumes) was allowed to interact in aqueous solution with methylamine and acetone for half an hour, when it was found that tropinone was formed:



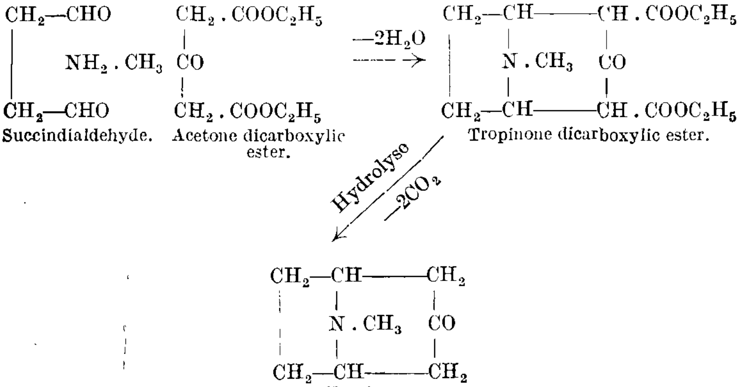
Succindialdehyde. Acetone. Tropinone.

Better yields can be obtained by substituting for acetone the ester or calcium salt of acetone dicarboxylic acid. The intermediate product is a tropinone dicarboxylic acid from which two molecules of carbon dioxide can be split off by acidifying and heating the solution—

* The Greek ψ is used instead of the word "pseudo." Thus ψ-tropine represents pseudo-tropine.

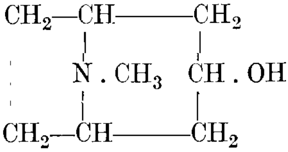
[1] Willstätter, *Annalen*, 1901, **317**, 268; 1903, **326**, 1; *Ber.*, 1901, **33**, 3163; Willstätter and Iglauer, *ibid.*, 1900, **33**, 1170.

[2] Robinson, *J.*, 1917, **111**, 762.



Tropinone.

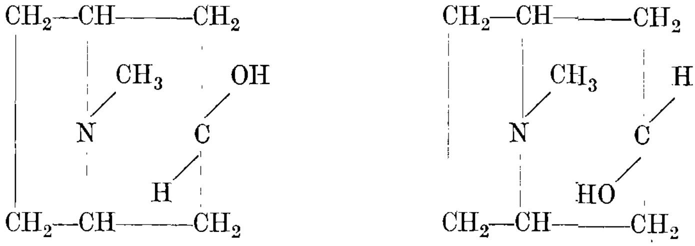
From tropinone, tropine itself can be obtained[1] by the action of zinc dust and concentrated hydriodic acid :



Tropine.

The isomerism of tropine and ψ-tropine may be explained very simply. If the space formula of a compound having the constitution of tropine be built up, it will be found that there are two possibilities : the hydroxyl and the methyl groups may lie on the same side of the ring as in (A), or on opposite sides as in (B) :

(A.) (B.)



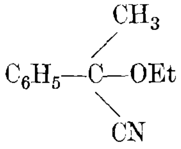
Of the two, tropine is the labile isomer, so that we can convert it at will into ψ-tropine.

[1] Willstätter and Iglauer, *Ber.*, 1900, **33**, 1170.

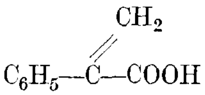
2. *Tropic Acid.*

By the synthesis of tropine we have approached that of another alkaloid, atropine. This substance, when boiled with baryta water, breaks down into tropine and tropic acid. We have thus established the constitution of half the atropine molecule; and in the present section we shall deal with the constitution of the other portion.

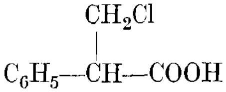
Tropic acid has been synthesized by Ladenburg and Rügheimer.[1] Acetophenone is treated with pentachloride of phosphorus, whereby the oxygen atom is replaced by two chlorine ones, and acetophenone chloride is formed. This is allowed to react with potassium cyanide in alcoholic solution to form the nitrile of atrolactinic ethyl ether:



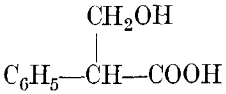
The nitrile is then hydrolyzed, forming the acid. When this body is boiled with concentrated hydrochloric acid it loses alcohol, and is converted into atropic acid:



Hydrochloric acid then attaches itself to the double bond, yielding *β*-hydrochloratropic acid:



This substance, when boiled with potassium carbonate, exchanges a chlorine atom for a hydroxyl group, and is converted into tropic acid:

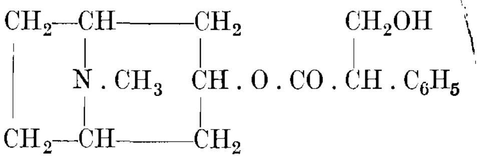


Tropic acid.

[1] **Ladenburg** and Rügheimer, *Ber.*, 1880, **13**, **376**, **2041**.

3. *Atropine and Hyoscyamine*

The constitutions of the two halves of the atropine molecule have now been established, and the atropine synthesis can be carried out by treating a mixture of tropine and tropic acid with hydrochloric acid gas in the usual way.[1] Atropine, therefore, is the tropine ester of *dl*-tropic acid, and it must have the constitution shown by the following formula :—



Atropine.

When tropine is esterified with *lævo*-tropic acid instead of the racemic acid, a substance is obtained which proves to be identical with the naturally-occurring alkaloid hyoscyamine.[2] Hyoscyamine is therefore the *dl*-tropine ester of *dl*-tropic acid and is a stereoisomer of atropine.

4. *Ecgonine*

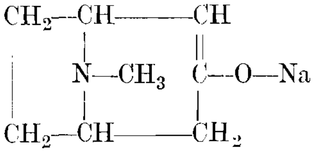
Tropinone forms salts with alkalis, and these, by treatment with carbon dioxide in the usual way, can be converted into the alkali salts of carboxylic acids.[3] In the case of the sodium salt, it is suspended in ether, and carbon dioxide is passed through the liquid at ordinary temperatures; the resulting product is the sodium salt of tropinone carboxylic acid, and when this is reduced with sodium amalgam in a weakly acid solution it yields a mixture of two isomeric bodies having the same composition as ecgonine, $C_8H_{14}NO$. COOH.

The two isomers, however, differ in character. The one has all the properties of ecgonine, except the power of rotating the plane of polarization ; it is a true carboxylic acid, forming salts and esters, it also possesses a free hydroxyl group, and can be converted into esters by acids. The second isomer, on the

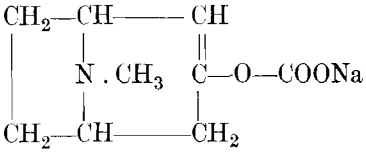
[1] Ladenburg, *Ber.*, 1879, **12**, 941 ; 1880, **13**, 104.
[2] Amenomiya, *Arch. Pharm.*, 1902, **240**, 498 ; compare Barrowcliff and Tutin, *J.*, 1909, **85**, 1969.
[3] Willstätter and Bode, *Ber.*, 1900, **33**, 411.

other hand, behaves quite differently. It possesses no free hydroxyl group ; nor can it be esterified by the ordinary methods. An explanation of the formation of two such substances is to be found by considering the character of the sodium derivative of tropinone.

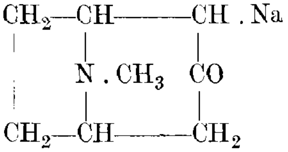
It is well known that the sodium salts of ketonic bodies usually exist in the enolic form, so that we should incline to write the formula of the tropinone sodium salt thus :

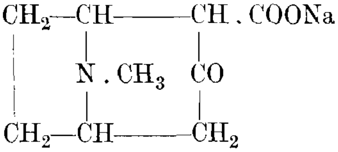


The action of carbon dioxide upon this would produce a sodium salt whose constitution could be written :

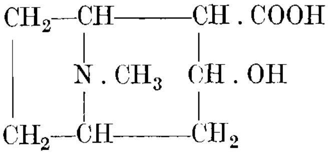


This body forms by far the greater proportion of the reaction mixture, but since the sodium salt of tropinone exists in the keto- as well as in the enol-form, part of the end-product will have the constitution shown below :





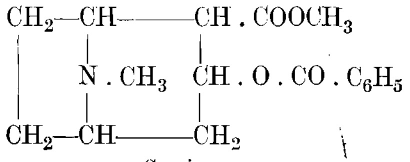
This last substance, on reduction, would give us the alcohol :



which proves to be racemic ecgonine.

5. *Cocaine*

From ecgonine, cocaine can be prepared by benzoylating the alcohol radicle, and then esterifying the carboxyl group with methyl alcohol :



Cocaine.

6. *Hyoscine*

The hyoscine section of the tropine group has suffered from confusion of nomenclature. Originally the name hyoscine was applied to tropine itself. Thereafter it was used to designate an alkaloid extracted from mother-liquors during the preparation of hyoscyamine. At a still later stage, this last-named alkaloid was found to be identical with another, derived from *Scopolia japonica* and hence termed scopolamine. The word scopolamine was next applied to *dl*-hyoscine, which had previously been christened atroscine. These vagaries of nomenclature may be disregarded here ; and the name hyoscine employed throughout to distinguish the alkaloid with which we are about to deal.

Hyoscine, obtained from *Datura metel*, is a lævo-rotatory compound with the composition $C_{17}H_{21}O_4N$. On hydrolysis, it yields tropic acid and a base oscine * which has the composition $C_8H_{13}O_2N$. Since the constitution of tropic acid has already been elucidated, the only unknown portion of the hyoscine molecule is the oscine fragment, which will now be examined.

When oscine, $C_8H_{13}O_2N$, is heated to 130° C. with hydrobromic acid, it yields [1] hydrobromoscopoline hydrobromide, $C_8H_{14}O_2NBr . HBr$, which, on reduction,[2] is converted into dihydroscopoline, $C_8H_{15}O_2N$.

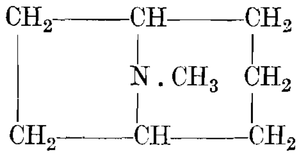
Dihydroscopoline contains two hydroxyl groups, so that its formula can be written $C_8H_{13}(OH)_2N$. Now tropane has the composition $C_8H_{15}N$, which suggests that dihydroscopoline may

* Also termed scopoline.

[1] Schmidt, *Apoth. Zeit.*, 1902, **17**, 592.

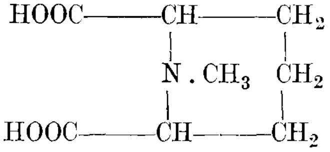
[2] Schmidt, *Arch. Pharm.*, 1905, **243**, 559.

be a dihydroxy-tropane. This proves to be the case, for on reduction [1] with phosphonium iodide and hydriodic acid at 200° C. it yields tropane:



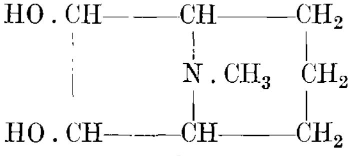
Tropane.

The structure of dihydroscopoline will therefore be known as soon as the positions of the two hydroxyl radicles have been ascertained. Now on oxidation with chromic acid,[2] dihydroscopoline yields N-methyl-piperidine-2 : 6-dicarboxylic acid (scopolic acid).



Scopolic acid.

Since the hydroxyl groups disappear in this reaction, it is clear that they must have been attached to the carbon atoms which now form the nuclei of the carboxyl groups; and dihydroscopoline obviously has the structure:

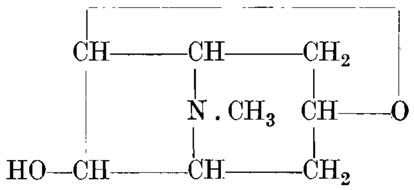


Dihydroscopoline.

It is now necessary to work back from dihydroscopoline to oscine. Since there is a difference of two hydrogen atoms between the compositions of the substances, obviously dihydroscopoline is the dihydro-derivative of oscine; and the problem seems near solution. It is, however, not so simple as it appears. Dihydroscopoline contains two hydroxyl radicles; oscine has two oxygen atoms but only one hydroxyl group. Clearly

[1] Hess, *Ber.*, 1918, **51**, 1007.
[2] Hess, *Arch. Pharm.*, 1909, **247**, 79.

oscine must contain an oxygen bridge which is opened up by the addition of the two hydrogen atoms ; for no other hypothesis will fit the case since oscine is neither an aldehyde nor a ketone. Two suggestions have been put forward with regard to the probable position of this oxygen bridge. Hess[1] postulated a propylene-oxide ring in the molecule, whilst King[2] proposed a butylene-oxide structure which is now generally accepted.[3]



Oscine.

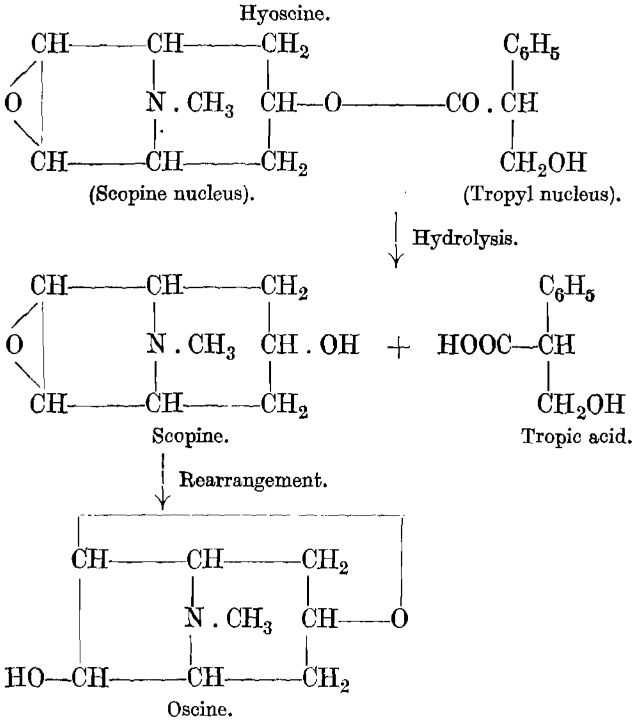
Examination of this oscine formula will, however, reveal a difficulty. It contains no fewer than five asymmetric carbon atoms. Now King[4] observed that oscine can be resolved into *d*- and *l*-forms, whilst benzoyl-oscine can also be separated into optically antipodal forms ;[5] but *dl*-hyoscine yields only two stereoisomeric forms, the optical rotatory powers of which arise from the tropic acid portion of the molecule. This could be explained on either of two hypotheses.[6] The first of these postulates that the three known forms of hyoscine correspond respectively to *d*-tropyl-*dl*-oscine, *l*-tropyl-*dl*-oscine, and *dl*-tropyl-*dl*-oscine. In view of the large number of stereoisomerides which can be derived from a molecule containing five asymmetric carbon atoms, this suggestion can hardly be regarded as satisfactory. The second hypothesis assumed that hyoscine is not formed by the combination of tropic acid and oscine, but is derived from tropic acid and an isomer of oscine having a symmetrical structure and capable of changing into oscine in the hydrolysis of hyoscine.

This second hypothesis is probably the correct explanation

[1] Hess, *Ber.*, 1918, **51**, 1007.
[2] King, *J.*, 1919, **115**, 476.
[3] Gadamer and Hammer, *Arch. Pharm.*, 1921, **259**, 110 ; Hess and Wahl, *Ber.*, 1922, **55**, 1972.
[4] King, *J.*, 1919, **115**, 476.
[5] Tutin, *J.*, 1910, **97**, 1793.
[6] King, *J.*, 1919, **115**, 476.

of the phenomena. Hess and Wahl [1] were unable to prepare *l*-hyoscine by esterifying *l*-tropic acid with *dl*-oscine, which shows that *l*-hyoscine is not *l*-tropyl-*dl*-oscine, although *dl*-oscine is formed from it on hydrolysis. Willstätter and Berner [2] completed the proof in the following way. By hydrolyzing hyoscine with pancreatic lipase in presence of ammonium chloride as a buffer salt, they obtained a new material, scopine, $C_8H_{13}O_2N$. This substance is obviously an isomer of oscine, as the formula shows; and it is readily converted into oscine by either acid or alkali. Scopine is therefore the real basic product in the hydrolysis of hyoscine, and the observed production of oscine in this reaction is due to the conversion of the initially-formed scopine into its isomer.

In order to account for the facts, the following formulæ have been proposed.



[1] Hess and Wahl, *Ber.*, 1922, **55**, 1972.
[2] Willstätter and Berner, *Ber.*, 1923, **56**, 1079.

Inspection will show that the scopine molecule is symmetrical and should therefore be optically inactive—as is found in practice. Since the rearrangement into oscine occurs after the active tropic acid has been removed by hydrolysis, nothing corresponding to an asymmetric synthesis can occur ; and the oscine thus formed will also be inactive, just as is found by experiment. The structure assigned to hyoscine above, therefore, seems in agreement with the facts.

CHAPTER XI

THE QUINOLINE AND ISOQUINOLINE ALKALOIDS

A.—The Quinoline Group

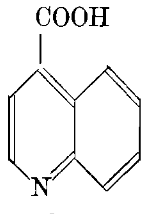
1. *The Constitution of Cinchonine*

The alkaloid cinchonine has the composition $C_{19}H_{22}ON_2$. The oxygen atom forms part of a hydroxyl group, as is shown by acetylation ; and the two nitrogen atoms are tertiary ones.

I. When cinchonine is oxidized by means of chromic acid and sulphuric acid [1] it breaks down into two substances, cinchonic acid and meroquinene, in accordance with the following equation :—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 3O = \underset{\text{Cinchonic acid.}}{C_{10}H_7O_2N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

Cinchonic acid has been shown to be a quinoline carboxylic acid of the formula—

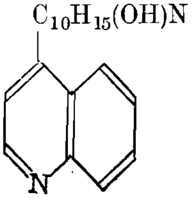


so that cinchonine itself must be a γ-quinoline derivative.

For the sake of convenience, we shall refer to the two halves of the cinchonine molecule as the " quinoline half " and the " second half." It is obvious that the hydroxyl group which is known to exist in the cinchonine molecule must be situated in the " second half " ; for if it were in the " quinoline half " it

[1] Königs, *Ber.*, 1894, **27**, 1501.

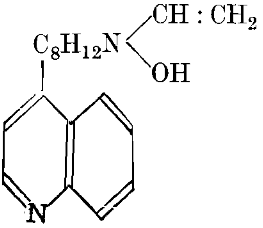
would appear in cinchonic acid. Cinchonine may therefore be formulated in the following way :—



II. Now, when cinchonine is oxidized with potassium permanganate [1] instead of chromic acid, the decomposition products are quite different from those obtained before. The reaction takes the course shown below—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 4O = \underset{\text{Cinchotenine.}}{C_{18}H_{20}O_3N_2} + H.COOH$$

This new oxidation product, cinchotenine, contains the quinoline nucleus (as is shown by its behaviour on further oxidation). It is therefore produced by a decomposition in the "second half" of the molecule. It contains a hydroxyl and a carboxyl group. Cinchonine can take up one molecule of a halogen acid, but cinchotenine has lost this property. Hence the group CH_2 of cinchonine has been split off, leaving the carboxyl group in cinchotenine. We may thus carry our deductions a step further, and write the formula of cinchonine thus :—



III. When cinchonine is treated with phosphorus pentachloride and then with alcoholic potash it loses a molecule of water and is converted into cinchene : [2]

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} - H_2O = \underset{\text{Cinchene.}}{C_{19}H_{20}N_2}$$

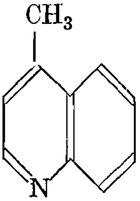
When heated with 25 per cent. phosphoric acid,[3] cinchene

[1] Königs, *Annalen*, 1879, **197**, 374.
[2] Comstock and Königs, *Ber.*, 1884, **17**, 1985.
[3] Königs, *Ber.*, 1890, **23**, 2677 ; 1894, **27**, 900.

takes up two molecules of water and is decomposed into lepidine and meroquinene :

$$\underset{\text{Cinchene.}}{C_{19}H_{20}N_2} + 2H_2O = \underset{\text{Lepidine.}}{C_{10}H_9N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

Lepidine is known to have the formula :



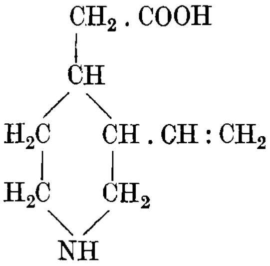
IV. Meroquinene is the next substance whose decompositions must be examined. When it is oxidized with an ice-cold mixture of sulphuric acid and potassium permanganate it gives cincholoiponic acid : [1]

$$\underset{\text{Meroquinene.}}{C_9H_{15}O_2N} + 4O = \underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + H.COOH$$

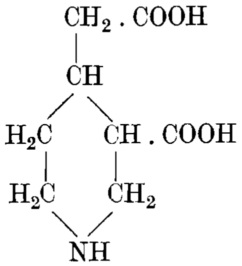
This, by the action of aqueous permanganate, is converted into loiponic acid : [2]

$$\underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + O_2 = \underset{\text{Loiponic acid.}}{C_7H_{11}O_4N} + H.COOH$$

Loiponic acid is an unstable form of hexahydrocinchomeronic acid, for on heating with caustic potash it is converted into that substance by isomeric change. By assuming the *structure* of loiponic acid to be the same as that of hexahydrocinchomeronic acid (the *configurations* of the two being different), it is possible to work back step by step to meroquinene, whose formula must therefore be that shown in the series below :



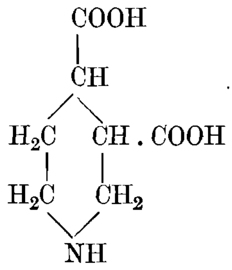
Meroquinene.



Cincholoiponic acid.

[1] Königs, *Ber.*, 1895, **28**, 1986, 3150.

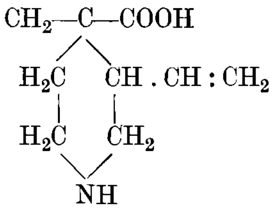
[2] Skraup, *Monatsh.*, 1896, **17**, 377 ; Königs, *Ber.*, 1897, **30**, 1329.



Loiponic acid.

The position of the $—CH_2 . COOH$ group of meroquinene is uncertain.

The formula above is due to Königs, but the alternative put forward by Miller and Rohde : [1]



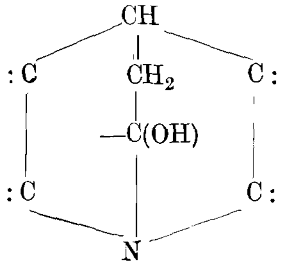
has probably as much to recommend it.

Of the ten carbon atoms of the " second half " we have thus established the mode of linkage of eight : five in a piperidine ring, two in a vinyl group, and one in a methyl or methylene group. The ninth carbon atom of the " second half " must be utilized in joining the two halves together. Thus we have only to determine the position of the tenth carbon atom of the " second half."

V. It will be remembered that the two nitrogen atoms of cinchonine are tertiary ; but it has been shown that the nitrogen atom of meroquinene is a secondary one. This has been established by the usual reactions of the imido-group, and agrees with the constitution ascribed to meroquinene in the previous paragraph. This peculiar behaviour of the nitrogen atom can best be explained by the assumption that in the " second half " of cinchonine there is a nucleus of either of the types (I.) or (II.) :

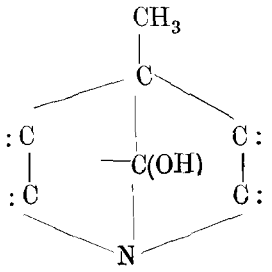
[1] Miller and Rohde, *Ber.*, 1895, **28**, 1060.

Königs' view.



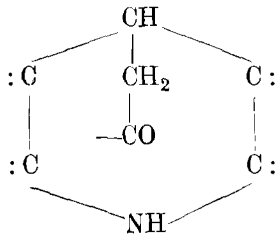
(I.)

v. Miller's view.

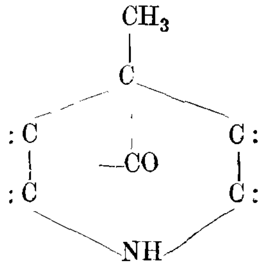


(II.)

When such a nucleus as (I.) is heated with dilute acids it will undergo intramolecular change into an imido-ketone in the way expressed by the formula (I*a*.) below. If the type (II.) be chosen instead of (I.) the analogous substance (II*a*.) would be produced in the same way :



(I*a*.)

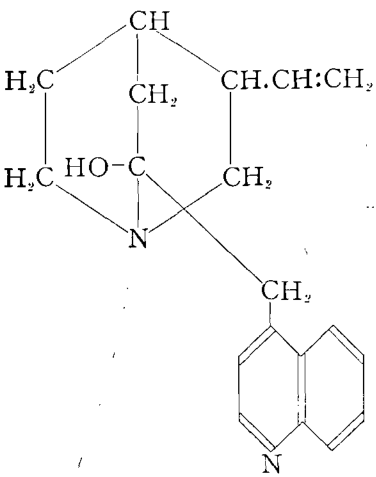


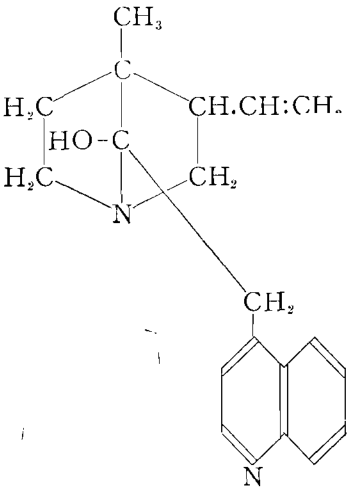
(II*a*.)

Such a change actually occurs when cinchonine is heated with dilute acetic acid ; an imido-ketone results, which, on account of its poisonous properties, is named " *cinchotoxine*." [1] Thus it is apparent that across the piperidine ring there is a bridge, and this accounts for the missing tenth carbon atom in the " second half " of cinchonine.

From the foregoing evidence, cinchonine would be represented by either of the two formulæ below :

[1] Miller and Rohde, *Ber.*, 1894, **27**, 1187, 1279 ; 1895, **28**, 1056.





2. *The Constitution of Quinine*

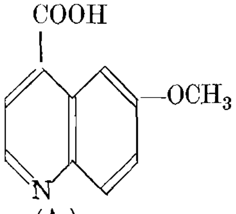
Knowing the constitution of cinchonine, we can easily prove that of quinine.

I. Quinine differs from cinchonine by one carbon, one oxygen, and two hydrogen atoms :

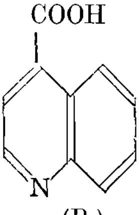
$$\underset{\text{Quinine.}}{C_{20}H_{24}O_2N_2} - \underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} = CH_2O$$

This points to quinine being a methoxy-derivative of cinchonine, if the similarity in character between the two substances is borne in mind.

II. When oxidized with sulphuric and chromic acids,[1] quinine gives the acid (A) ; whereas it will be remembered that cinchonine gave cinchonic acid (B). Meroquinene is one of the oxidation products in both cases—



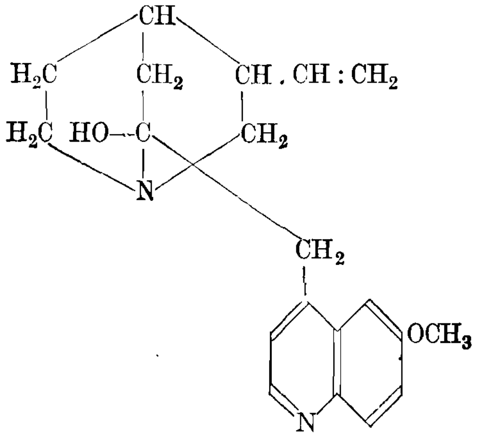
(A.)



(B.)

[1] Skraup, *Monatsh.*, 1881, **2**, 591 ; 1883, **4**, 695 ; 1891, **12**, 1106 ; 1895, **16**, 2684

III. This proves the presence and position of the methoxyl group in quinine; and since in its reactions quinine forms an exceedingly close analogue to cinchonine, we are justified in concluding that it is a methoxy cinchonine of the following constitution (accepting Königs' view of the structure of cinchonine) :—



Quinine.

3. *Cinchonidine and Conchinine*

Cinchonine has three asymmetric carbon atoms in its molecule, and therefore it may occur in several stereoisomeric forms. Chinchonidine is supposed to be one of these; while conchinine is a stereoisomer of quinine.

B.—The Isoquinoline Group

1. *The Constitution of Papaverine*

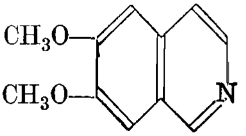
The constitution of papaverine is a much simpler question than that of cinchonine. There are six steps in the argument.[1]

I. In the first place, the formula of papaverine is $C_{20}H_{21}O_4N$; it contains four methoxyl groups, which can be hydrolyzed, yielding the substance papaveroline, $C_{16}H_9N(OH)_4$. This accounts for all the oxygen atoms.

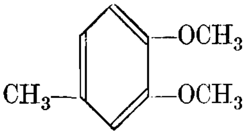
II. On fusion with alkali, papaverine breaks down into two

[1] Goldschmiedt, *Monatsh.*, 1883, **4**, 704; 1885, **6**, 372, 667, 954; 1886, **7**, 485; 1887, **8**, 510; 1888, **9**, 42, 327, 349, 679, 762, 778; 1889, **10**, 673, 692.

nuclei, one of which contains nitrogen, while the other nucleus is nitrogen-free. The first was proved to be a dimethoxy-*iso*-quinoline of the constitution :



while the second decomposition product was **dimethoxy-homocatechol** :

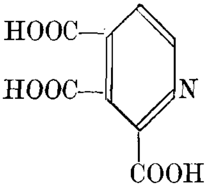


III. The fact that these two groups are *directly* united to one another follows from the composition of the two decomposition products :

$$H_2 + \underset{\text{Papaverine.}}{C_{20}H_{21}O_4N} = \underset{\substack{\text{Dimethoxy-}\\ \textit{iso}\text{-quinoline.}}}{C_{11}H_{11}O_2N} + \underset{\substack{\text{Dimethoxy-}\\ \text{homocatechol.}}}{C_9H_{12}O_2}$$

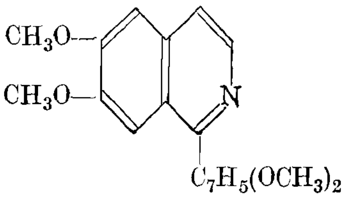
IV. We must now examine the question of the manner in which the two nuclei are united. Since papaverine contains four methoxy-groups, and each of the decomposition products contains two, it is obvious that during the decomposition no methoxy-group is destroyed. Now, if the link between the two nuclei had been an oxygen atom, *i.e.* if papaverine had contained the grouping R—O—CH_2—O—R, then in the breakdown of the molecule one -O . CH_3 . O- group would have been destroyed. We may therefore exclude the idea of joining the two nuclei through an oxygen atom, and must assume that they are directly united, carbon to carbon.

V. The next problem is to find which carbon atom of the isoquinoline ring is joined to the other nucleus. When papaverine is oxidized with potassium permanganate, the result is α-carbocinchomeronic acid :

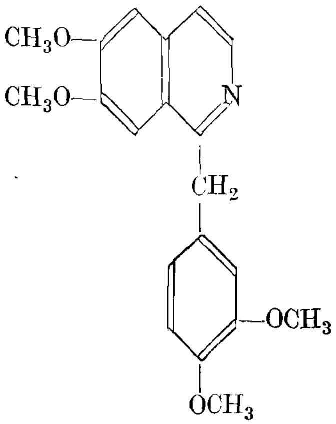


*

Hence we infer that the side-chain (second nucleus) was attached at the point now occupied by the carboxyl group, which is marked with an asterisk. Papaverine is therefore :



VI. We have now to settle the constitution of the group —$C_7H_5(OCH_3)_2$. This must be the dimethoxy-homocatechol radicle, which has the same composition. We have only to decide whether the two nuclei are joined ring to ring or by the intermediation of the side-chain of the dimethoxy-homocatechol. Without going into details, it may be said that all the evidence points to the union being made through the side-chain. The constitution of papaverine is therefore :



Papaverine.

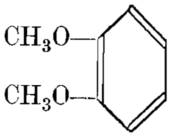
2. *The Synthesis of Papaverine*

The synthesis of papaverine was carried out by Pictet and Gams.[1] The reactions may be grouped in five stages.

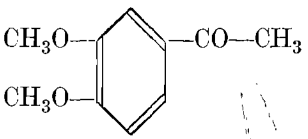
1. The first step in the process was the synthesis of amino-aceto-veratrone. For this purpose veratrol (I.) was treated with

[1] Pictet and Gams, *Compt. rend.*, 1909, **149**, 210.

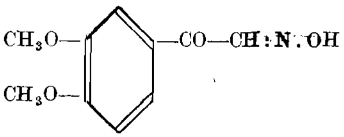
acetyl chloride in presence of aluminium chloride, whereby aceto-veratrone (II.) was formed. When this is treated with sodium ethylate and amyl nitrite, it yielded the isonitroso-derivative (III.), which was then reduced by tin chloride and hydrochloric acid to the hydrochloride of amino-aceto-veratrone (IV.) :



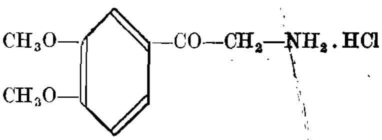
(I.)



(II.)

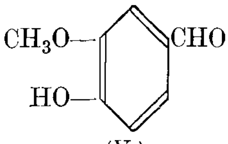


(III.)

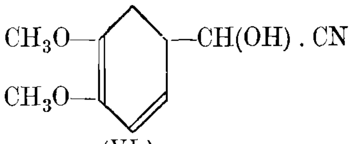


(IV.)

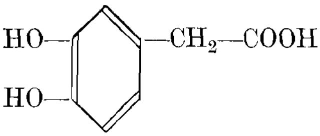
II. We must now turn to the synthesis of homoveratroyl chloride. Vanillin (V.) was methylated and then treated with hydrocyanic acid, giving dimethoxy-mandelic nitrile (VI.). When this was boiled with hydriodic acid three processes took place simultaneously : reduction, hydrolysis, and the splitting off of methyl radicles. Homoprotocatechuic acid (VII.) was thus obtained and by methylation of the hydroxyl groups, followed by the action of phosphorus pentachloride, the chloride of homoveratric acid was formed (VIII.) :



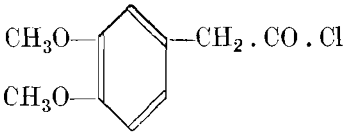
(V.)



(VI.)

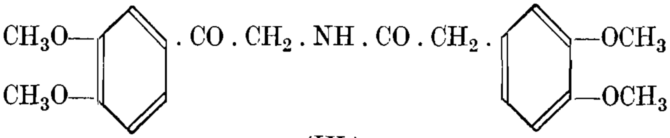


(VII.)



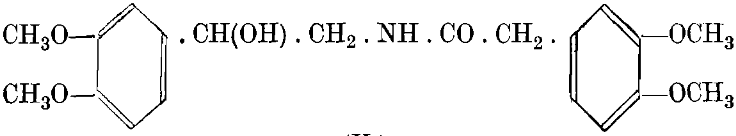
(VIII.)

III. If the amino-aceto-veratrone hydrochloride obtained in Stage **I.** be allowed to interact with the homoveratric chloride of Stage **II.** in presence of alkali, homoveratroyl-amino-aceto-veratrone (IX.) is formed.



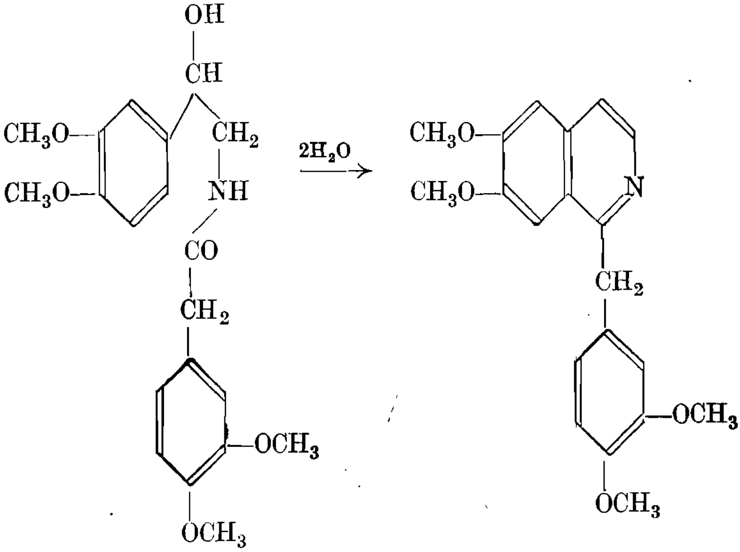
(IX.)

IV. An inspection of the formula (IX.) will show that though the substance contains two carbonyl groups, one of these is a true carbonyl while the other is a radicle which originally formed part of a carboxyl group. When the substance was reduced with sodium amalgam in neutral alcoholic solution, the true carbonyl was reduced, while the acidic carbonyl remains unaffected. The product was homoveratroyl-hydroxy-homoveratrylamine (X.) :



(X.)

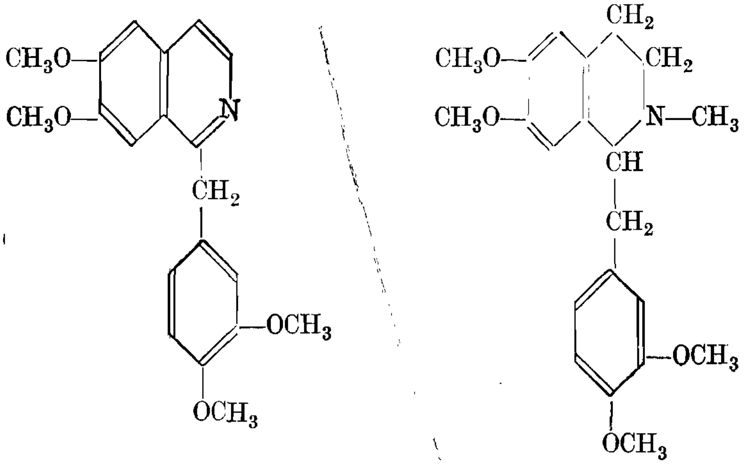
V. When this substance (X.) was treated with phosphorus pentoxide in boiling xylene solution, it lost two molecules of water and was converted into papaverine (XI.) :



(X.) (XI.)

3. *The Synthesis of Laudanosine*

Laudanosine is very simply produced from papaverine. Pictet and Athanasescu [1] showed that when the chloro-methyl derivative of papaverine is reduced with tin and hydrochloric acid methyl-tetrahydro-papaverine is formed. This synthetic substance is of course racemic ; and from it the dextro-antipode was obtained in the usual way by making the quinic acid salt of the alkaloid and fractionally crystallizing it. The substance thus obtained was found to be identical with natural laudanosine :



Papaverine. Laudanosine.

Pictet and Finkelstein [2] carried out the complete synthesis of laudanosine ; but as the method is very similar to that already described in the case of papaverine, we need not enter into it here.

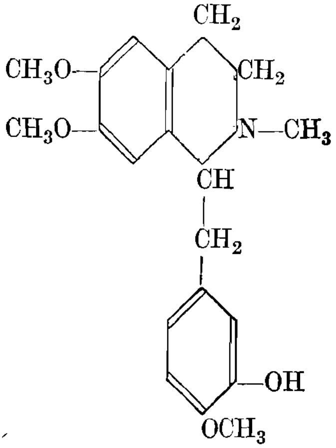
Laudanine contains one methyl group less than laudanosine ; but since there are four methoxy-groups in the structure of the latter alkaloid, there was considerable uncertainty on the subject until Späth and Lang [3] settled the matter by carrying out a synthesis on the usual lines but using chloroformic ester to shield a hydroxyl group during the reactions. The hydroxyl

[1] Pictet and Athanasescu, *Ber.*, 1900, **33**, 2346.

[2] Pictet and Finkelstein, *Ber.*, 1909, **42**, 1979 ; *Compt. rend.*, 1909, **148**, 925.

[3] Späth and Lang, *Monatsh.*, 1921, **42**, 273.

group was freed from the carbomethoxy radicle at the end of the process. In this way it was shown that laudanine was :



Laudanine.

Natural laudanine is dextro-rotatory. Two other substances occur also in opium and were regarded as independent alkaloids : tritopine and laudanidine. These have now been shown to be simply the lævo-form of laudanine.[1]

4. *Opianic Acid*

Though opianic acid itself is not an alkaloid, its constitution must be taken up at this point owing to its relation with narcotine, with which we shall deal later.

I. When narcotine is hydrolyzed with barium hydrate or sulphuric acid,[2] it decomposes into opianic acid and hydrocotarnine :

$$C_{22}H_{23}O_7N + H_2O = C_{10}H_{10}O_5 + C_{12}H_{15}O_3N$$

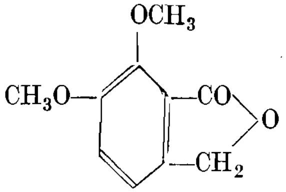
Narcotine. Opianic acid. Hydrocotarnine.

II. Opianic acid is a monobasic acid, and therefore we may write its formula $C_9H_9O_3 \, . \, COOH$.

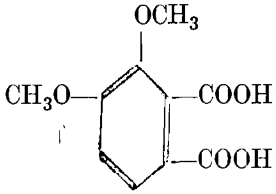
III. When heated with hydriodic acid, two methyl groups are split off from opianic acid.[3] It therefore contains two methoxy-groups, and may be written thus, $(CH_3O)_2 \, . \, C_7H_3O \, . \, COOH$.

[1] Späth and others, *Ber.*, 1925, **58**, 200, 1272.
[2] Beckett and Wright, *J.*, 1875, **28**, 583.
[3] Matthiessen and Foster, *Annalen Suppl.*, I., 333 ; II., 378 ; V., 333.

IV. When heated with potash[1] it gives (by reduction) meconine, and (by oxidation) hemipinic acid—



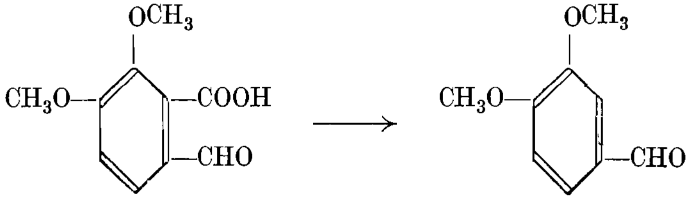
Meconine.



Hemipinic acid.

This last reaction is parallel to the formation of benzyl alcohol and benzoic acid by the action of potash upon benzaldehyde, so we must conclude that opianic acid contains an aldehydic group ; and from the constitution of hemipinic acid it is obvious that this aldehyde radicle must be next the carboxyl group of opianic acid.

V. The final proof of the presence of an aldehyde group in opianic acid is furnished by the behaviour of its sodium salt when distilled with soda-lime.[2] Carbon dioxide is split off in the usual way, and the methyl ether of vanillin is left. The formula of opianic acid must therefore be that which is shown below :



Opianic acid. Methyl ether of vanillin.

5. *The Constitution of Cotarnine*

The next stage in the proof of the narcotine constitution is reached through the constitution of cotarnine. This substance[3] is obtained along with opianic acid when narcotine is treated with oxidizing agents.

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + O + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Cotarnine.}}{C_{12}H_{15}O_4N}$$

[1] Matthiessen and Foster, *Annalen Suppl.*, I., 332 ; II., 381.

[2] Beckett and Wright, *J.*, 1875, **28**, 583.

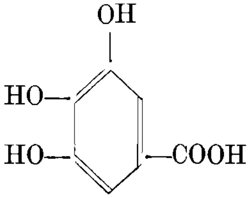
[3] Wöhler, *Annalen*, 1844, **50**, 1.

I. Cotarnine reacts with two molecules of methyl iodide, thus proving that it is a secondary base. The reaction product is called cotarnomethine methyl iodide,[1] and has the composition $C_{11}H_{11}O_4N(CH_3)_3I$.

II. By heating this body with caustic soda, trimethylamine is split off,[2] and cotarnone, $C_{11}H_{10}O_4$, remains. This proves to be an aldehyde, so that its formula can be written $C_{10}H_9O_3 . CHO$.

III. When cotarnone is oxidized with potassium permanganate [3] it gives a lactone, cotarnolactone, $C_{11}H_{10}O_6$, from which, on further oxidation, cotarnic acid, $C_{10}H_8O_7$, is obtained.

IV. By the usual reactions it is found that cotarnic acid [4] is dibasic, contains a methoxyl radicle, and has its carboxyl groups in the ortho-position to one another, as is shown by the ease with which it forms an anhydride. When heated with phosphorus and hydriodic acid to about 160° C. it yields gallic acid :

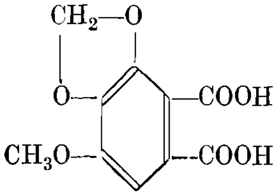


V. Now, gallic acid differs from cotarnic acid by the group $C_3H_2O_2$:

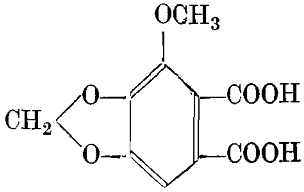
$C_{10}H_8O_7$	$-\ C_7H_6O_5$	$=\ CH_2$	$+\ CO_2$	$+\ C$
Cotarnic acid.	Gallic acid.	From methoxy-group.		

Part of this we can account for by the loss of carbon dioxide from a carboxyl group, since cotarnic acid is dibasic, while gallic acid is monobasic. This leaves one carbon atom unaccounted for. This must be derived from the methylene group of a methylene ether. We are in this way led to formulate cotarnic acid as a methyl-methylene-gallic-carboxylic acid, $C_6H(OCH_3)(CH_2O_2)(COOH)_2$. For such a substance there are only two possible formulæ :

[1] Roser, *Annalen*, 1888, **249**, 157.
[2] *Ibid.*, 141.
[3] *Ibid.*, 163.
[4] *Ibid.*, 163 ; 1899, **254**, 341.

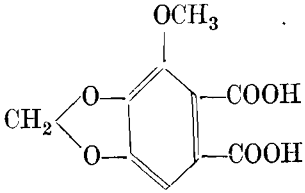


(I.)



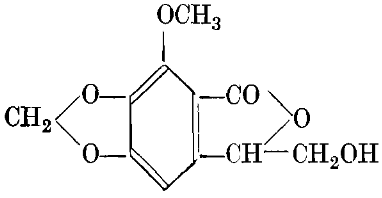
(II.)

Without going into details,[1] it may be said that the general behaviour of the substance is best represented by (II.). Cotarnic acid therefore has the constitution—

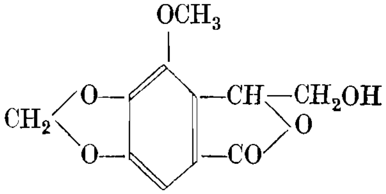


Cotarnic acid.

VI. Cotarnolactone must therefore have **either of the formulæ**:



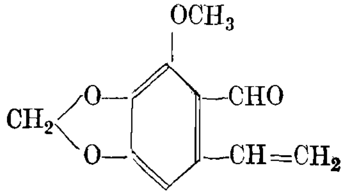
(I.)



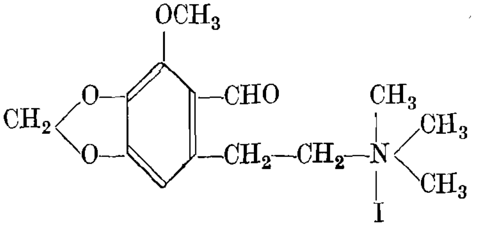
(II.)

As will be seen from the synthesis of cotarnine in the following section, the formula (I.) is correct; and cotarnone must be—

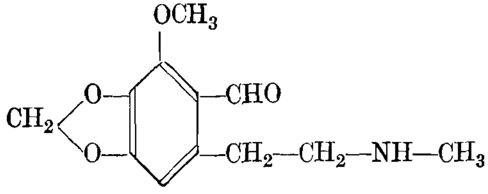
[1] Freund and Becker, *Ber.*, 1903, **36**, 1521.



VII. But cotarnone was obtained from cotarnomethine methyl iodide and soda, hence cotarnomethine methyl iodide must have the structure :

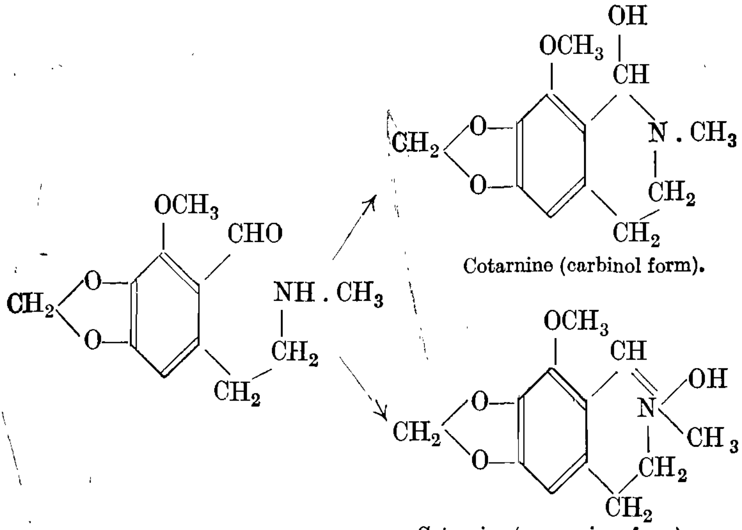


VIII. Hence cotarnine should have the following constitution ; since cotarnomethine methyl iodide is obtained from it by the action of two molecules of methyl iodide.



IX. This formula, however, fails to explain the formation of a pyridine derivative, apophyllenic acid, when cotarnine is oxidized with nitric acid ;[1] and to account for this it must be assumed that the free aldehydic group has disappeared in the course of some intramolecular ring-formation, which simultaneously brings into existence a pyridine chain within the molecule of cotarnine. This change may be represented in two ways, as shown in the formulæ below :

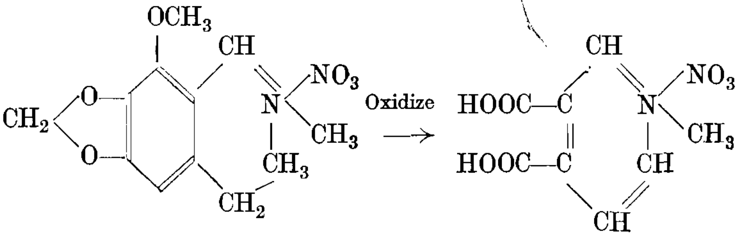
[1] Wöhler, *Annalen*, 1844, **50**, 24.



Cotarnine (carbinol form).

Cotarnine (ammonium form).

It is generally agreed that the salts of cotarnine are best represented as derivatives of the ammonium form ; for instance, the production of apophyllenic acid can be made clear on this assumption :



Cotarnine nitrate. Apophyllenic acid derivative.

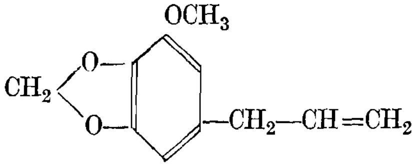
With regard to the free base, however, the spectroscopic investigations of Dobbie, Lauder, and Tinkler [1] have shown that the structure varies with the solvent in which the substance is dissolved. In ether or chloroform the carbinol form is present ; but the addition of alcohol to the solution brings into existence the ammonium form ; in pure alcoholic solution no less than 25 per cent. of the substance is present as ammonium base.

[1] Dobbie, Lauder, and Tinkler, *J.*, 1903, **83**, 598.

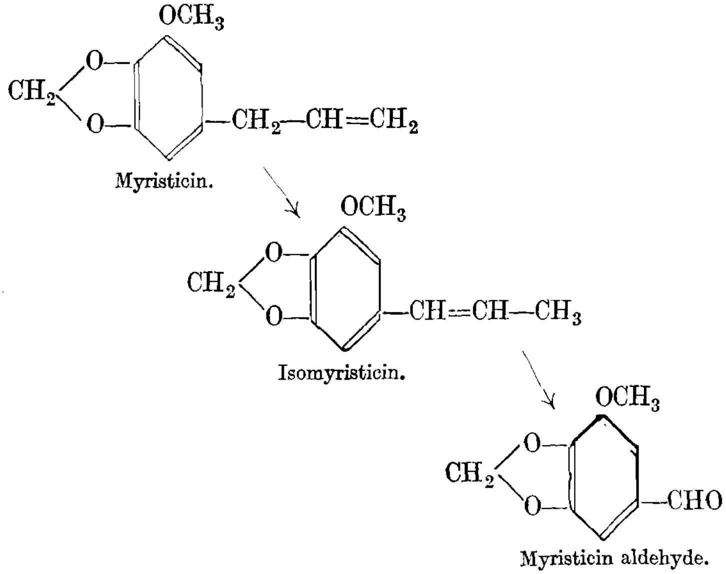
6. *The Synthesis of Cotarnine*

Synthetic cotarnine has been prepared by Salway;[1] but as the constitution of one of his intermediate products is left doubtful in the synthesis, it is not possible to establish the cotarnine structure from his work. In the light of the facts given in the last section, however, the formulæ of the intermediate compounds can be inferred.

I. The first stage in the process is the synthesis of β-3-methoxy-4 : 5-methylenedioxy-phenyl-propionic acid. Salway took as his starting point the substance myristicin—

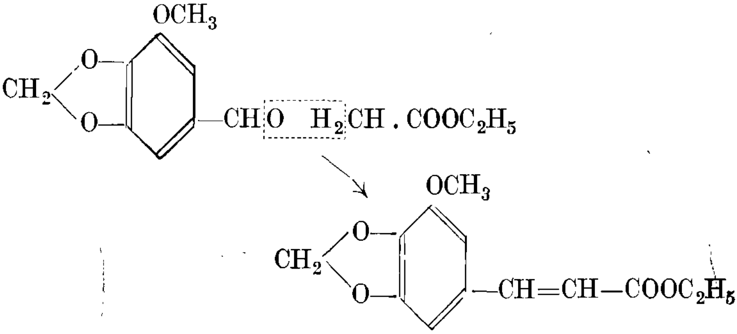


which he obtained from oil of nutmeg. This was heated with alcoholic potash to convert it into iso-myristicin; and the latter was then oxidized to myristicin aldehyde by means of potassium permanganate:

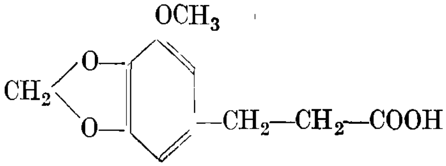


[1] Salway, *J.*, 1910, **97**, 1208.

The aldehyde was then condensed with ethyl acetate by means of sodium, and the resulting ester was hydrolyzed with alcoholic potash :

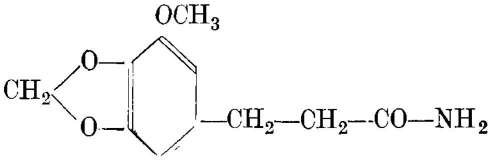


The substituted cinnamic acid thus produced was reduced with sodium amalgam, and in this way the required β-3-methyoxy-4 : 5-methylenedioxy-phenyl-propionic acid was obtained.

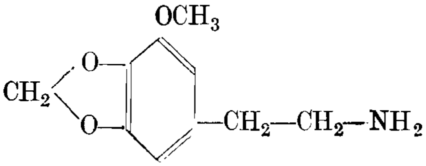


(I.)

II. The second stage ends in the production of phenyl-acetyl-β-3-methoxy-4 : 5-methylenedioxy-phenyl-ethylamine. The acid (I.) was converted into the amide (II.) in the usual way, and this in turn was changed into the corresponding amine (III.) by Hofmann's reaction :

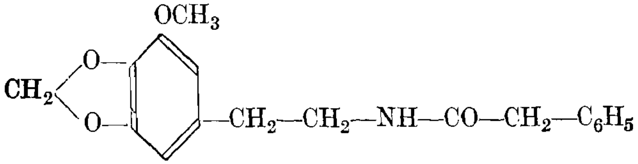


(II.)



(III.)

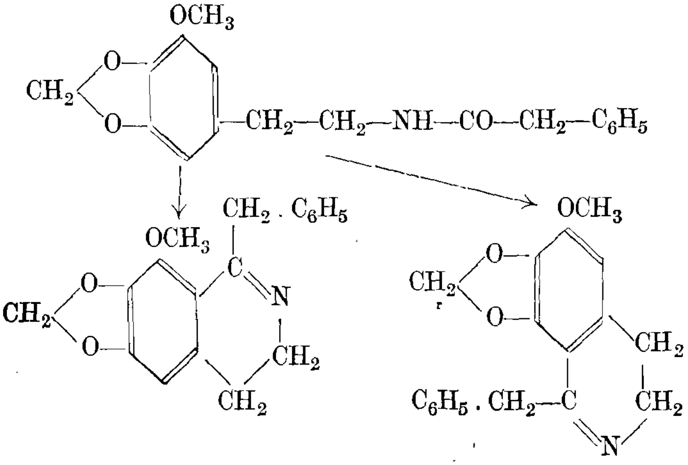
The phenylacetyl derivative (IV.) was then prepared by the ordinary method—



(IV.)

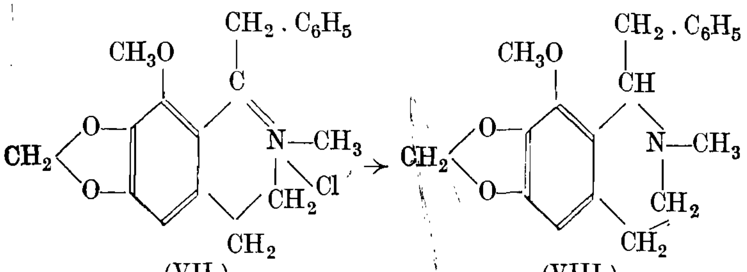
Phenylacetyl-β-3-methoxy-4 : 5-methylenedioxy-phenyl-ethylamine.

III. This phenylacetyl derivative was condensed by heating it with phosphoric oxide in presence of xylene ; and in this way a mixture of two isomeric dihydro-isoquinoline derivatives was produced (V. and VI.).



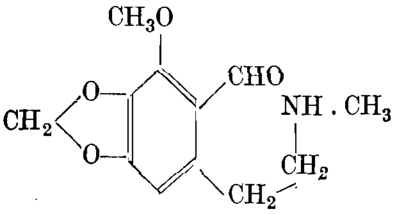
(V.) (VI.)

IV. The substance (V.) is 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro-isoquinoline. To convert it into cotarnine, it is necessary in the first instance to form its metho-chloride (VII.), which is then reduced by means of tin and hydrochloric acid to 1-benzyl-hydrocotarnine (VIII.).



(VII.) (VIII.)

Finally, oxidation with manganese dioxide in presence of sulphuric acid converted the benzyl derivative into cotarnine:

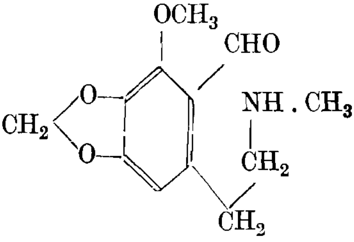


Cotarnine.

It will be noticed that the substance (VI.), if treated in the same way as (V.), would give rise to an iso-cotarnine; and if the cotarnine constitution were unknown, this synthesis would throw no light upon the relative positions of the methoxy-group and the pyridine ring.

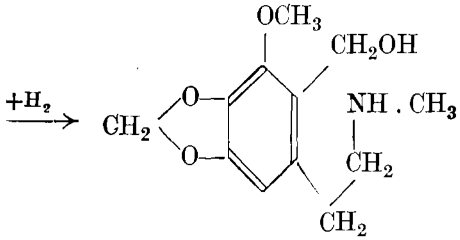
7. *The Synthesis of Hydrocotarnine*

On reduction, cotarnine is converted into hydrocotarnine,[1] which is formed in the manner indicated by the formulæ below:

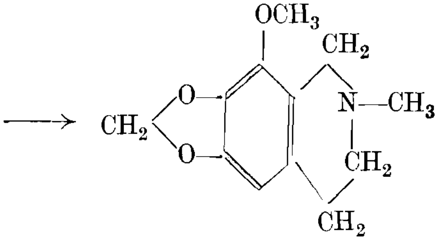


Cotarnine.

[1] Beckett and Wright, *J.*, 1875, **28**, 577; Bandow and Wolffenstein, *Ber.*, 1898, **31**, 1577.



Alcohol.



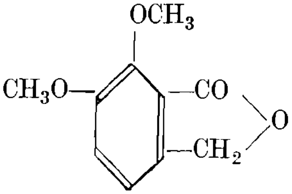
Hydrocotarnine.

8. *The Constitution of Narcotine*

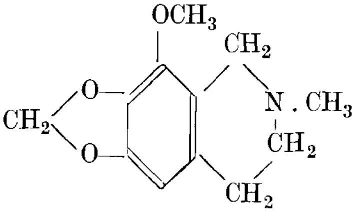
We have in the course of the previous sections amassed the material which is required in a consideration of the narcotine formula. Narcotine contains no carboxyl or hydroxyl radicle. It is made up of one hydrocotarnine nucleus and one opianic acid nucleus, the latter being in the form of the lactone, meconine. This is shown by the action of reducing agents upon narcotine:

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2 = \underset{\text{Meconine.}}{C_{10}H_{10}O_4} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N}$$

The mode of linkage of these two nuclei must now be considered. When the formulæ of meconine and hydrocotarnine are examined,



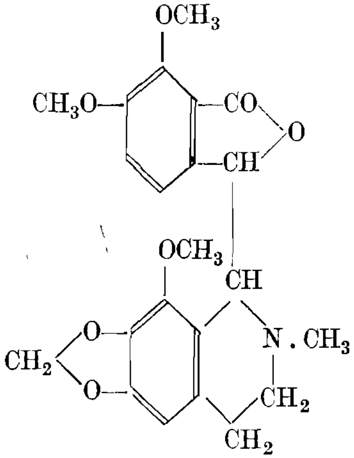
Meconine.



Hydrocotarnine.

it is obvious that the linking does not take place through an

oxygen atom, as all of these are fully occupied. It must, therefore, occur by the conjunction of two carbon atoms, each of which loses a hydrogen atom in the union. The pair of atoms which are most likely to be concerned in the linkage are those which give rise to the aldehyde groups of opianic acid and cotarnine, so that the formula of narcotine would be written :



Narcotine.

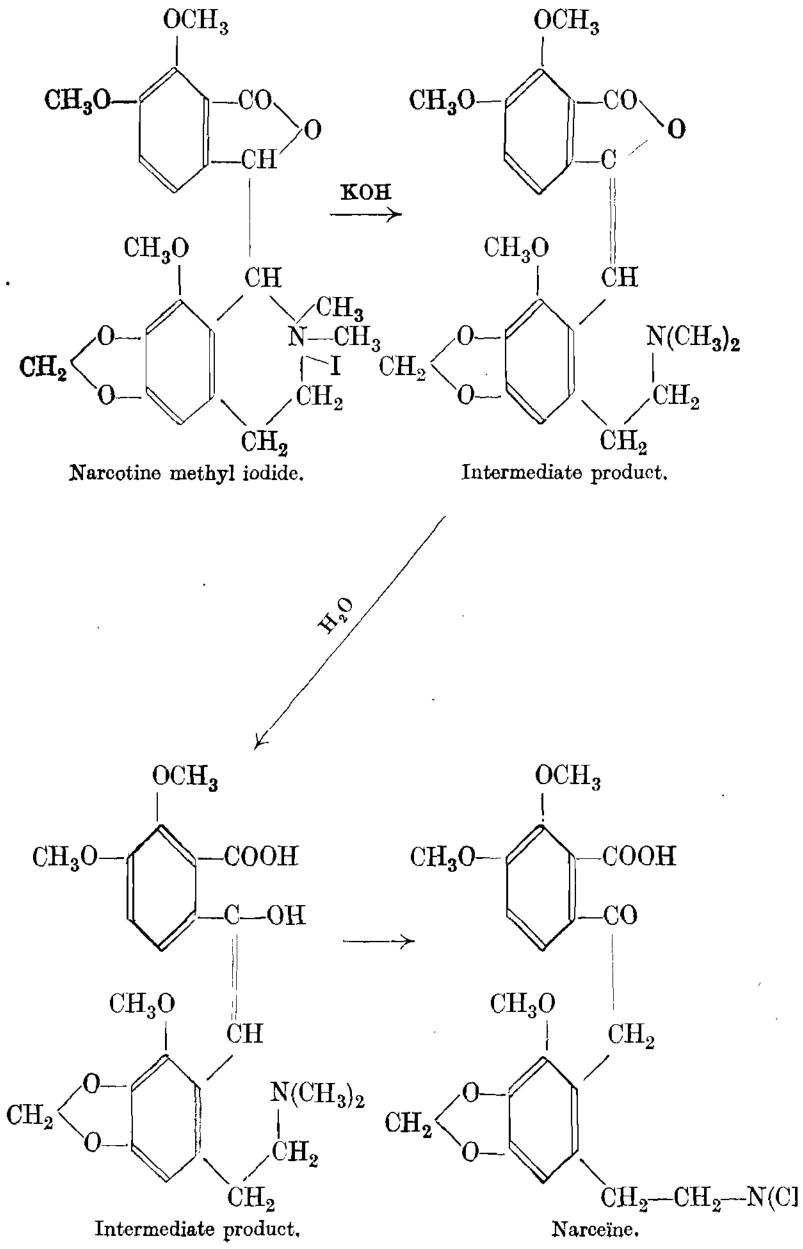
9. *The Syntheses of Gnoscopine and Narcotine*

Perkin and Robinson [1] showed that when cotarnine and meconine are boiled in alcoholic solution in presence of potassium carbonate the substance produced is identical with the alkaloid gnoscopine ; and by fractionally crystallizing the *d*-bromocamphorsulphonate of the base [2] they were able to isolate the dextro and lævo forms of narcotine, gnoscopine being the racemic variety. The lævo-narcotine thus obtained was identical with the natural alkaloid.

10. *The Synthesis of Narceïne*

When the methyl iodide addition product of narcotine is treated with alkalis, it is converted into a substance narceïne, which was first called pseudo-narceine.[3] The course of the reaction may be formulated in the following way :—

[1] Perkin and Robinson, *P.*, 1910, **26**, 46.
[2] *Ibid.*, 131.
[3] Roser, *Annalen*, 1888, **247**, 167 ; 1889, **254**, 357 ; Freund and Frankforter, *ibid.*, 1893, **277**, 31.


KOH
H_2O
Narcotine methyl iodide.
Intermediate product.
Intermediate product.
Narceïne.

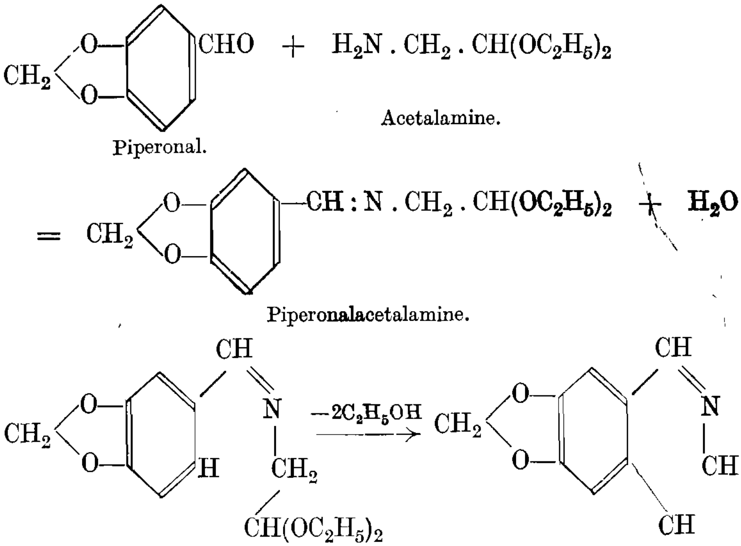
11. *The Synthesis of Hydrastinine*

This substance, which occurs among the decomposition products of the alkaloid hydrastine, has been synthesized by Fritsch;[1] and as a knowledge of its constitution will help us in our consideration of the hydrastine formula, we may give a brief account of Fritsch's work before dealing with the natural alkaloid.

When chloracetal is treated with ammonia, it yields the substance acetalamine, which has the formula:

$$NH_2 \,.\, CH_2 \,.\, CH(OC_2H_5)_2$$

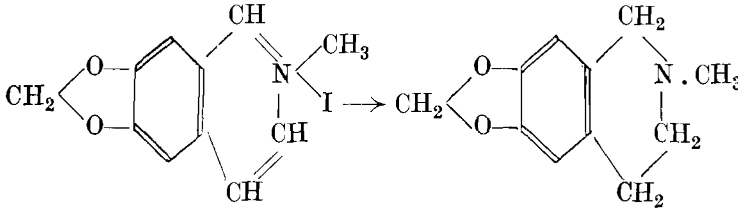
This substance can be made to condense with aromatic aldehydes; and when the products thus obtained are treated with sulphuric acid, alcohol is split off and isoquinoline derivatives are formed. If this reaction be applied to the case of piperonal, the following series of reactions take place:—



Piperonalacetalamine. Methylenedihydroxyisoquinoline.

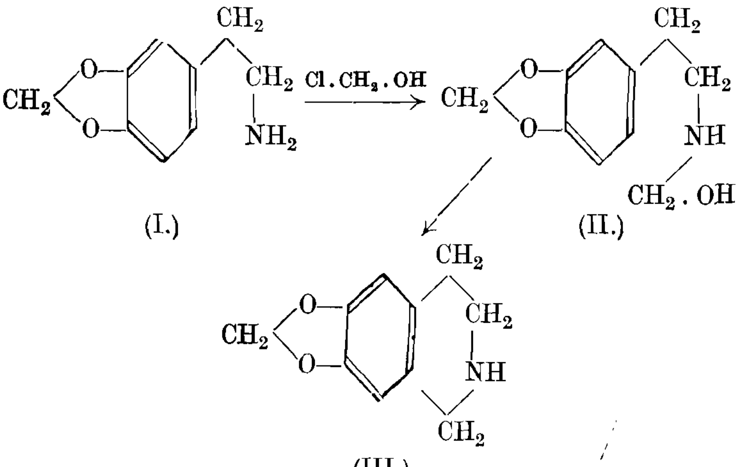
When the methyl iodide addition product of this body is reduced by means of tin and hydrochloric acid, it gives the substance hydrohydrastinine:

[1] Fritsch, *Annalen*, 1895, **286**, 18.



Iodomethylate. Hydrohydrastinine.

A simpler synthesis is due to Rosenmund.[1] In ethereal solution, chloromethyl alcohol acts upon homopiperonylamine (I.) to form homopiperonylaminomethanol (II.) which, when treated with 10 per cent. aqueous hydrochloric acid yields dihydro-norhydrastinine (III.) from which hydrohydrastinine can be obtained :



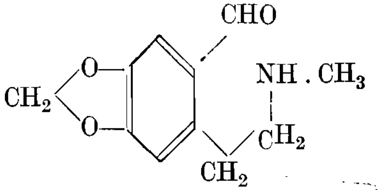
(I.) (II.) (III.)

Freund [2] has converted hydrohydrastinine into hydrastinine by oxidizing it with potassium bichromate and sulphuric acid.

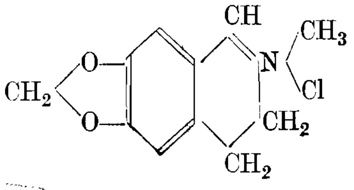
Now, from the fact that the behaviour of hydrastinine, on reduction and salt formation, closely resembles that of cotarnine,

[1] Rosenmund, *Ber. deut. pharm. Ges.*, 1919, **29**, 200.
[2] Freund, *Ber.*, 1887, **20**, 2403.

we are enabled to put forward the following structural formula for it :—



Hydrastinine.

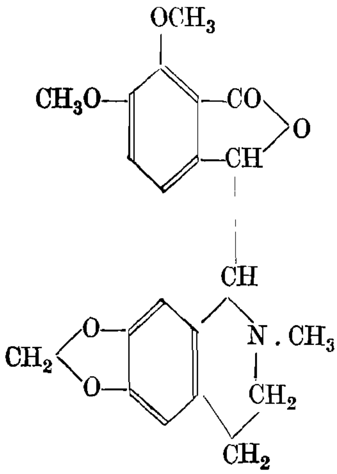


Hydrastinine hydrochloride.

This formula explains why hydrastinine behaves as an aldehyde, why it forms a ring-compound in presence of acids, why its salts contain one molecule of water less than the free base, why it yields apophyllenic acid on oxidation, and many other properties which the substance possesses. A comparison of their formulæ will show that cotarnine is a methoxylated hydrastinine.

12. *The Constitution of Hydrastine*

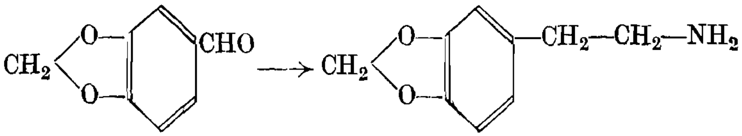
Hydrastine contains one methoxyl group less than narcotine, but in all other respects it resembles that compound. Now, on oxidation with dilute nitric acid, hydrastine breaks down into hydrastinine and opianic acid just as narcotine breaks down into cotarnine and opianic acid. But, as was shown in the preceding section, cotarnine is methoxy-hydrastinine, so that we may conclude that if we eliminate the methoxy-group from narcotine we shall have hydrastine. This actually proves to be the case; so that we may write the formula of hydrastine by simply taking that of narcotine and replacing the methoxyl radicle of the cotarnine half by a hydrogen atom. Hydrastine would therefore be :



Hydrastine.

13. *The Synthesis of Berberine*

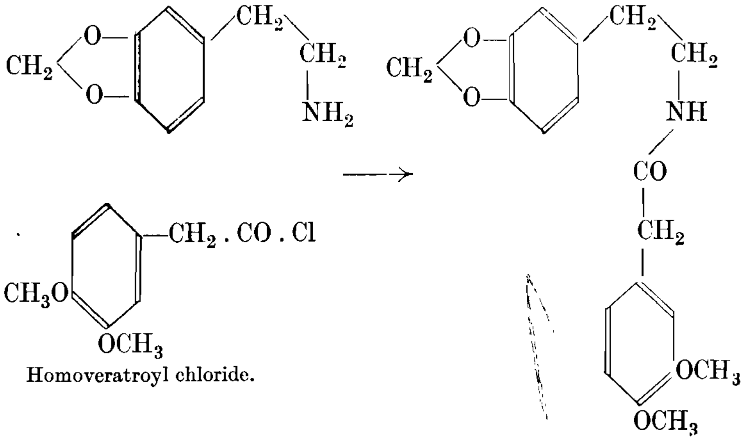
Piperonal (I.) forms the starting-point of this series of reactions. When it is condensed with nitromethane in presence of sodium methylate, it produces piperonylidene-nitromethane from which in turn homopiperonaldoxime and homopiperonylamine (II.) are obtained by reduction.[1]



(I.) (II.)

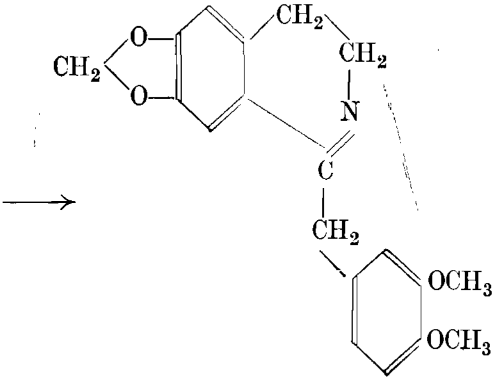
Homoveratroyl chloride (the preparation of which has already been described [2]) is now allowed to act upon the amine yielding a condensation product (III.), which loses one molecule of water when heated with phosphorus pentoxide in xylene solution forming (IV.):

[1] Bouveault and Wahl, *Compt. rend.*, 1902, **135**, 41; Medinger, *Monatsh.*, 1906, **27**, 237.
[2] See p. 237.



Homoveratroyl chloride.

(III.)

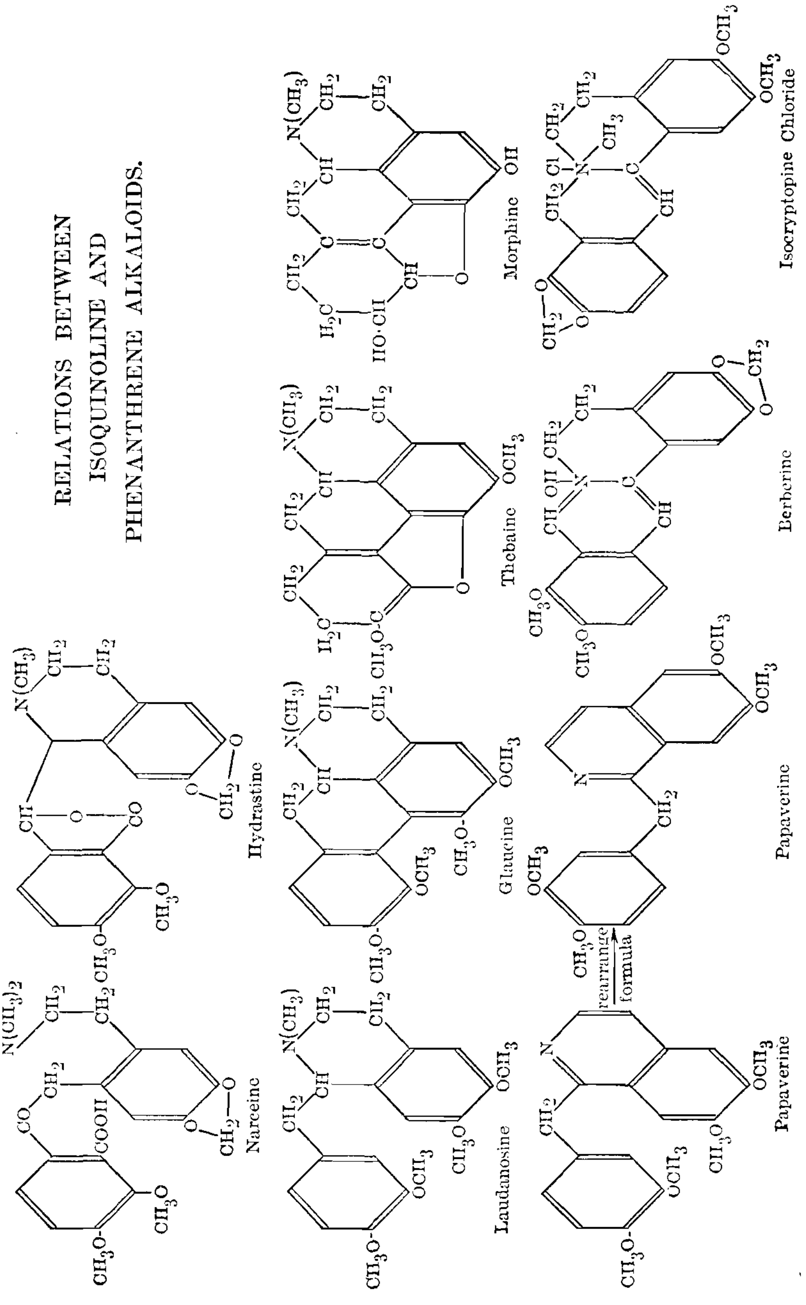


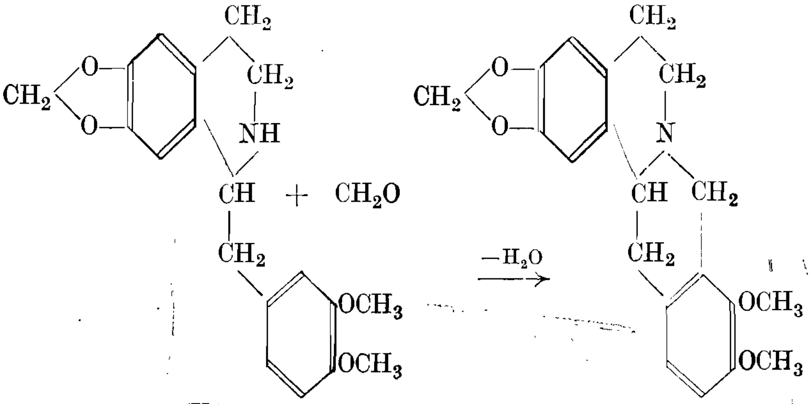
(IV.)

When the isoquinoline derivative (IV.) is reduced with tin and hydrochloric acid, it yields veratroyl-norhydrohydrastinine (V.). Condensation of the hydrochloride of this with methylal results in the entry of an extra carbon atom into the molecule, with the formation of a new six-membered ring. This produces tetrahydroberine ; [1] from which berberine itself is obtained by oxidation.[2]

[1] Pictet and Gams, *Compt. rend.*, 1911, **153**, 386 ; *Ber.*, 1911, **44**, 2480.
[2] Hlasiwetz and Gilm, *Annalen Supp.*, 1863, **2**, 191.

RELATIONS BETWEEN ISOQUINOLINE AND PHENANTHRENE ALKALOIDS.





(V.)

Tetrahydroberberine.

The true constitution of berberine is not yet agreed upon as there are several ways in which hydrogen might be removed from tetrahydroberberine.

14. *The General Relationship of Certain Alkaloids*

In the foregoing pages the constitutions of various alkaloids have been discussed ; but owing to the mass of detail required for the elucidation of the structure of these compounds, there is a considerable chance that the general relationships existing between the various compounds may have been overlooked by the reader. The table * on p. 258 will serve to bring into view not only the kinship between some of the alkaloids dealt with in the foregoing pages but also their relations with alkaloids of the phenanthrene group.

* I am indebted to Professor Collie for this table.

CHAPTER XII

THE PURINE * GROUP

1. *Introductory* [1]

THE members of the purine group offer many points of interest to the chemist; and before entering into a detailed account of the constitutions of the various compounds, it may be well to indicate some of the lines of investigation which touch upon this class of substances.

In the first place, purine derivatives are found as products of both animal and vegetable metabolism. Tea contains small proportions of caffeine, theophylline, xanthine, and adenine. Theobromine is found in cocoa; and hypoxanthine has been detected in black pepper. In some animal organisms, purine compounds appear to be the main end-product of protein decomposition; for snake-excrement contains up to 90 per cent. of uric acid. In human urine, quite marked amounts of various purine derivatives make their appearance.

A second field of interest is to be found in the pathological importance of uric acid. This substance is a normal product of human metabolism; but when its secretion exceeds the proper bounds, it becomes a dangerous material in the vital organism and gives rise to a number of diseases among which may be mentioned rheumatism and stone in the bladder. Its deleterious action is enhanced by the fact that it is very slightly soluble, and is thus difficult to eliminate from the body; and in order to facilitate its removal it is often necessary to administer to the patient either lithia water or doses of piperazine, since the

* This, like many other chemical terms, is what Lewis Carroll defined as a portmanteau word. It is derived from the two words *purum uricum.*

[1] Fischer's papers on the purine group have been collected under the title "*Untersuchungen in der Puringruppe* (1882–1906)," and the reader is referred to this work for further information.

lithium and piperazine salts of uric acid are more soluble than the ordinary metallic salts formed in the human organism.

Yet another region is touched when the biochemist attempts to determine the manner in which the purine derivatives are formed in Nature. It appears [1] that when the nucleic acids break up, adenine and guanine are the primary products; and that from them hypoxanthine and xanthine are then formed by secondary reactions. Further, the demethylation undergone in the human organism by the tea-alkaloids suggests interesting problems.[2]

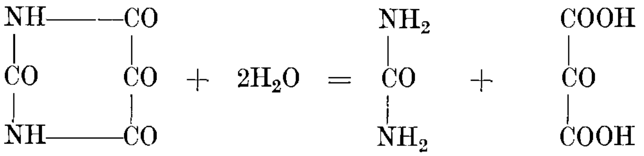
From the standpoint of therapeutics, the pharmacological action of such substances as caffeine, theobromine, and theophylline is of considerable importance.

Finally, on the purely chemical side, the unravelling of the constitutions of these intricate materials has furnished work for chemists of the front rank during a century and a half. It is obviously impossible, within the limits of the space available here, to deal in detail with all the work in this field. Only the merest outline can be given, but even that will be sufficient to suggest the complexity of the problem which presented itself when the purine group came under investigation.

2. *Uric Acid*

Uric acid has the composition $C_5H_4O_3N_4$.

On oxidation with cold nitric acid,[3] it yields alloxan, $C_4H_2O_4N_2$. Since alloxan, on hydrolysis, yields mesoxalic acid and urea, it is evidently the ureide mesoxalyl-urea.[4]

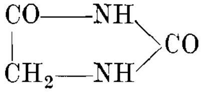


Alloxan. Urea. Mesoxalic acid.

The action of alkaline potassium permanganate upon uric acid [5] leads to the production of allantoin, $C_4H_6O_3N_4$, the skeleton

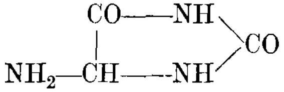
[1] Steudel, *Z. physiol. Chem.*, 1906, **48**, 408; Jones, *ibid.*, 1904, **41**, 101.
[2] Kruger and Salomon, *Z. physiol. Chem.*, 1898, **24**, 364; **26**, 350.
[3] Liebig and Wöhler, *Annalen*, 1838, **26**, 245.
[4] Liebig and Wöhler, *Annalen*, 1838, **26**, 256.
[5] Liebig and Wöhler, *Annalen*, 1838, **26**, 245.

of which is established by the following reactions. On reduction with hydriodic acid,[1] allantoin yields hydantoin :

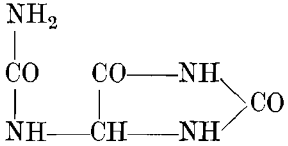


Hydantoin.

Allantoin therefore contains the hydantoin ring with a side-chain attached to it. The position of this side-chain is proved by the fact that by combined oxidation and reduction [2] allantoin yields 5-amino-hydantoin :

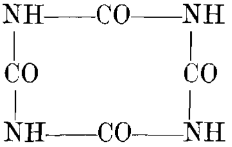


Further, this 5-amino-hydantoin regenerates allantoin on treatment with potassium cyanate, which suggests that allantoin has the structure : *



Allantoin.

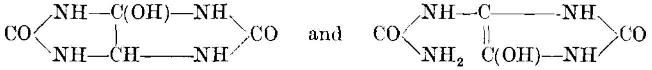
A final piece of evidence may be mentioned, though its value is not so great as the rest. On oxidation with hydrogen peroxide in alkaline solution,[3] uric acid yields a substance tetracarbonimide, $C_4H_4O_4N_4$, which is assumed to have the structure :



[1] Baeyer, *Annalen*, 1861, **117**, 178 ; 1864, **130**, 158.

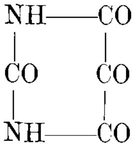
[2] Biltz and Giesler, *Ber.*, 1913, **46**, 3410.

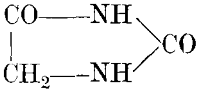
* The above formula contains an asymmetric carbon atom. Since allantoin from natural sources is found to be optically *inactive*, it is suggested that the compound can tautomerize into either of two forms, neither of which contains an asymmetric system :



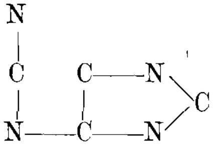
[3] Scholtz, *Ber.*, 1901, **34**, 4130 ; Schittenheim and Wiener, *Z. physiol. Chem.*, 1909, **62**, 102.

It is now possible to attempt the fitting together of the arious data in order to work back to the formula of uric acid.]vidently, the uric acid skeleton must contain the six-membered lloxan grouping and the five-membered hydantoin ring :



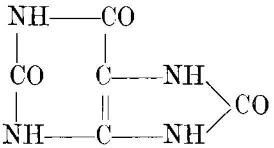


ince these two rings contain a total of seven carbon atoms, hereas uric acid has only five carbon atoms in all, it is clear ıat two of the carbon atoms must be joint members of both ngs. Couple this with the fact that uric acid must contain ıe allantoin skeleton :

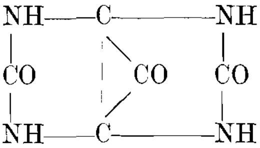


nd it is obvious that the only remaining point in doubt is the osition of the fifth carbon atom in uric acid.

Two formulæ were suggested, which are shown below :



Medicus's Formula.



Fittig's Formula.

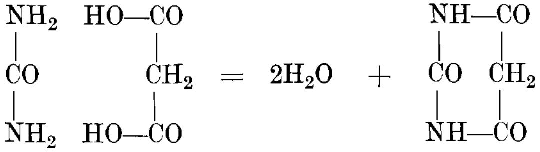
ow, since Fittig's formula is obviously symmetrical, it co eld only one N-methylated uric acid ; whereas the formula edicus admits of no less than four N-methyl-substituted ı cids. Since these four derivatives have actually been prepared, ittig's formula is known to be insufficient ; and the Medicus rmula[1] is accepted as being correct ; and it has been rengthened by various syntheses[2] of uric acid, two of which

[1] Medicus, *Annalen*, 1875, **175**, 236.

[2] Horbaczewski, *Monatsh.*, 1882, **3**, 796 ; 1885, **6**, 356 ; 1887, **8**, 201, 584 ; ehrend and Roosen, *Ber.*, 1888, **21**, 999 ; *Annalen*, 1889, **251**, 235 ; Traube, er., 1900, **33**, 1371, 3035 ; Fischer and Ach, *Ber.*, 1895, **28**, 2473 ; Fischer, *Ber.*, 897, **30**, 559.

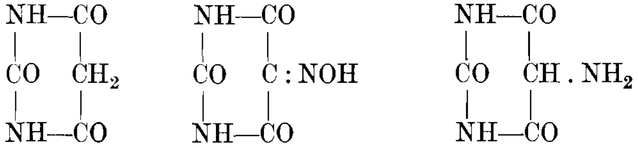
may now be described, the first due to Fischer, the second to Traube.

When malonic acid is treated with urea, it yields a cyclic ureide, malonyl-urea or barbituric acid :



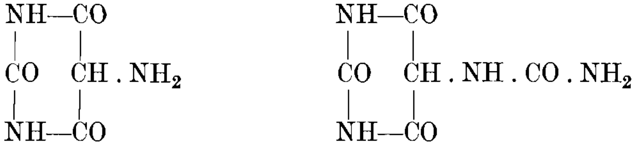
Barbituric acid.

By the action of nitrous acid, the methylene group of barbituric acid is replaced by the isonitroso-radicle in the usual way, giving oximido-malonyl-urea, which is also called violuric acid ; and on reduction of this substance the oximido-group is converted into an amido-radicle, producing amido-malonyl urea, or uramil :



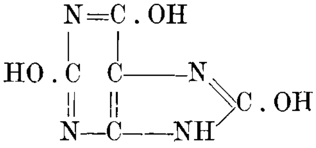
Barbituric acid. Violuric acid. Uramil.

On treatment with potassium cyanate, uramil takes up cyanic acid and is changed into pseudo-uric acid :

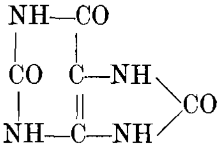


Uramil. Pseudo-uric acid.

It is very hard to extract water from pseudo-uric acid, but this can be done by heating it with molten oxalic acid or by boiling it with hydrochloric acid. Under these circumstances one molecule of water is lost and uric acid is produced. Its property of forming salts is ascribed to the existence of an enolic form, such as :

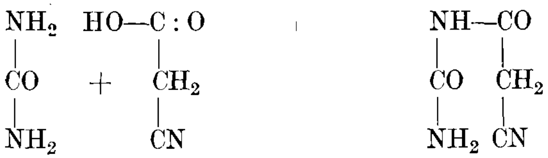


It is more usual, however, to consider uric acid to exist normally in the isomeric form :



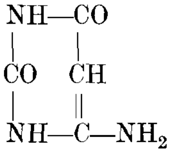
Uric acid.

The second synthesis of uric acid starts with the condensation of urea with cyanacetic acid, which takes place under the influence of phosphorus oxychloride :



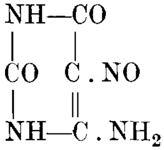
Cyanacetyl-urea.

Caustic soda causes cyanacetyl-urea to undergo an intramolecular change by which it is converted into amido-uracil :

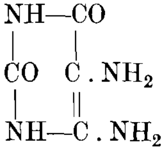


Amido-uracil.

When this is treated with nitrous acid it gives a nitroso-compound which can be reduced with ammonium sulphide to diamido-uracil :

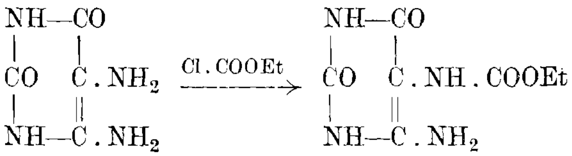


Nitroso compound.



Diamido-uracil.

The next step is to treat this diamido-derivative with caustic potash and chloroformic ester, by which means a urethane is formed :



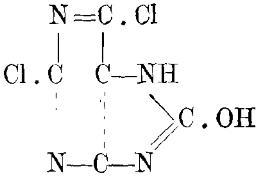
Diamido-uracil. Diamido-uracil urethane.

By heating the sodium salt of this substance to 180°–190° C. the sodium salt of uric acid is obtained.

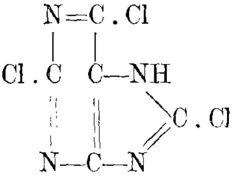
By adapting this last synthesis many uric acid derivatives can be obtained; for we may use substituted ureas instead of the parent substance, or we may replace the urea by guanidine, or, lastly, we may discard the chloroformic ester in favour of formic ester.

3. *Purine*

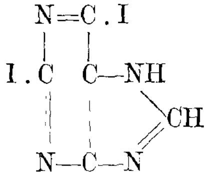
When the sodium salt of uric acid is treated with oxychloride of phosphorus it yields a hydroxy-dichloro-purine of the following formula:—



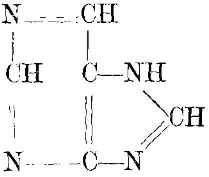
This, by means of trichloride of phosphorus, can be changed into a trichloro-derivative, the third hydroxyl group being replaced by a chlorine atom. The substance thus formed, trichloropurine, is then treated with hydriodic acid at 0° C. whereby di-iodopurine is produced. This by reduction with water and zinc dust, gives purine itself:



Trichloropurine.



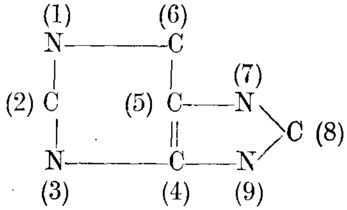
Di-iodopurine.



Purine.

Purine is the substance to which all the substances of the purine group are usually referred; the derivatives being

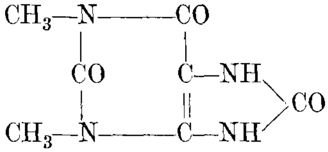
distinguished by means of the system of numbering shown in the following scheme :—



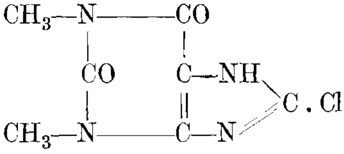
Purine skeleton.

4. *Theophylline*

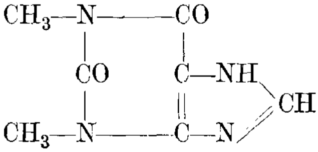
If in the uric acid syntheses symmetrical dimethyl-urea be employed instead of the parent substance, the product of the reactions is dimethyl-uric acid :



When this is treated with trichloride and oxychloride of phosphorus at 150° C. it is converted into a substance chlorotheophylline, one atom of chlorine replacing a hydroxyl group. Chlorotheophylline must, therefore, have the following constitution :



By reducing with hydriodic acid, theophylline[1] is formed:

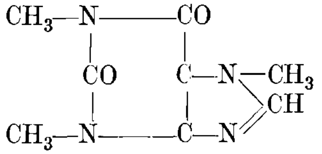


Theophylline.

[1] Fischer and Ach, *Ber.*, 1895, **28**, 3135

5. *Caffeine*

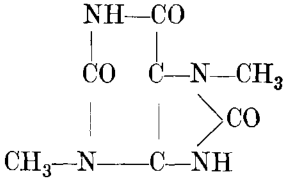
Caffeine is obtained by the action of methyl iodide upon theophylline.[1] Its constitution is therefore expressed by:



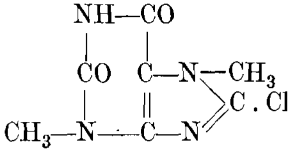
Caffeine.

6. *Theobromine*

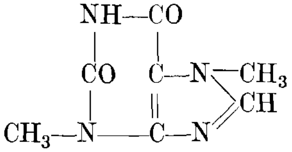
When the dimethyl-uric acid which has the constitution (I.) shown below is treated with phosphorus oxychloride, it gives chlorotheobromine (II.), which, on reduction with hydriodic acid, yields theobromine (III.).[2] The reactions are parallel to those which lead from the isomeric dimethyl-uric acid to theophylline:



(I.)



(II.)



Theobromine.

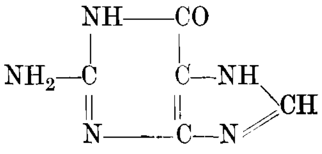
(III.)

7. *Guanine and Xanthine*

Guanine, $C_5H_5ON_5$, is found to constitute a large proportion of guano; and it is found also in the pancreas of certain animals. The simplest method of preparing it was devised by Traube,[3]

[1] Fischer and Ach, *Ber.*, 1895, **28**, 3135.
[2] Fischer, *Ber.*, 1897, **30**, 1839.
[3] Traube, *Ber.*, 1900, **33**, 1371.

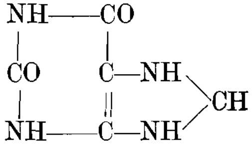
in which the starting materials are guanidine and cyanacetic ester. The reactions in this synthesis follow the same lines as in the Traube synthesis of uric acid, so it is unnecessary to give details in this place. The steps in the synthesis establish the constitution of guanine, which proves to be 2-amino-6-hydroxy-purine:



Guanine.

Guanine has been obtained also by heating 6-hydroxy-2:8-dichloro-purine with alcoholic ammonia and reducing the resulting chloro-guanine by means of hydriodic acid.[1]

When treated with nitrous acid, guanine is converted into xanthine:

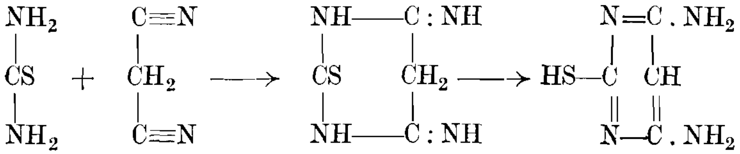


Xanthine.

As the formula shows, xanthine is capable of acting as 2:6-dihydroxy-purine.

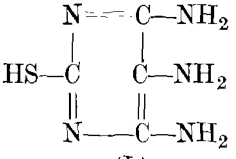
8. *Adenine and Hypoxanthine*

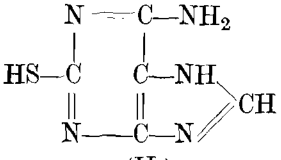
The structure of adenine is determined by the method of synthesis devised by Traube.[2] Thiourea and malononitrile are condensed together in presence of sodium ethylate, yielding 4:6-diamino-2-mercapto-pyrimidine:



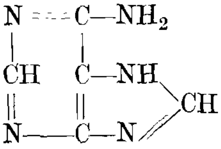
[1] Fischer, *Ber.*, 1897, **30**, 2251.
[2] Traube, *Annalen*, 1904, **331**, 69, 86.

By the action of nitrous acid, followed by reduction, this is converted into a tri-amino compound (I.), which is then acted on by formic acid to yield (II.):


(I.)


(II.)

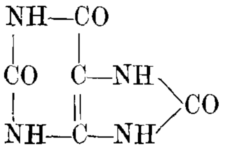
Oxidation of (II.) by means of hydrogen peroxide yields adenine:

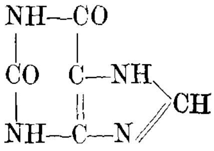

Adenine.

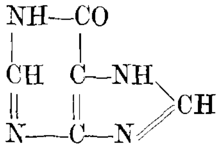
When treated with nitrous acid, adenine is converted into hypoxanthine, which is thus shown to have the constitution of purine with a hydroxyl group in the 6-position.

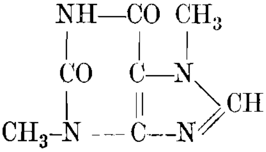
9. *Conclusion*

At this point it seems well to bring together all the formulæ of the purine derivatives which have been dealt with in the foregoing sections, so that the relations between them can be seen at a glance. The structures are given in the ketonic form, and the corresponding names based on the purine nomenclature are given in brackets.

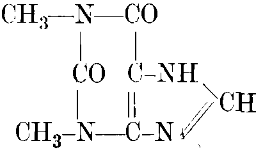

Uric acid (2 : 6 : 8-trihydroxypurine).


Xanthine (2 : 6-dihydroxypurine).

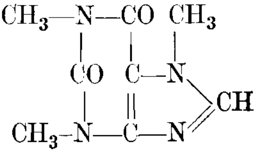

Hypoxanthine (6-hydroxypurine).



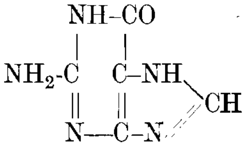
Theobromine
(3 : 7-dimethyl-2 : 6-dihydroxy-purine).



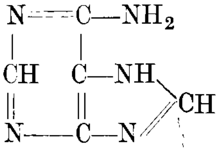
Theophylline
(1 : 3-dimethyl-2 : 6-dihydroxy-purine).



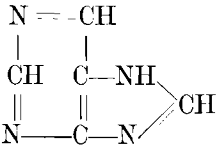
Caffeine
(1 : 3 : 7-trimethyl-2 : 6-dihydroxy-purine).



Guanine
(2-amino-6-hydroxy-purine).



Adenine
(6-amino-purine).



Purine.

CHAPTER XIII

THE POLYPEPTIDES [1]

1. *Introductory*

THE contents of the cells from which living tissues are built up are, for the most part, composed of albuminous bodies of extremely complicated chemical character. These albumins are distinguished from all the other naturally occurring substances by the fact that animal life may be supported upon them alone in conjunction with water and salt; whereas fats and carbohydrates do not in themselves furnish nourishment sufficient for the support of animal functions for an indefinite period. The importance of the albumins from the physiological point of view, therefore, can hardly be over-estimated; while from the chemical side they furnish one of the most difficult and complicated problems which the organic chemist has yet attacked.

The difficulties of the researches which have been carried out in this branch of organic chemistry can hardly be over-estimated. In the first place, many albumins are non-crystalline substances which require special treatment before they can be obtained in crystalline form; this, of course, makes it very difficult to determine the state of purity of any specimen under consideration. Secondly, the extreme sensitiveness of albumins to heat, acids, or alcohol renders them very liable to be altered during the progress of the ordinary chemical reactions. Again, the molecular complication of these substances must be tremendous, if we are to judge from molecular weight determinations: egg albumin has been estimated to have a molecular

[1] A complete set of references up to 1906 will be found in a lecture by Fischer (*Ber.*, 1906, **39**, 530). See also Fischer, *Ber.*, 1906, **39**, 2893; 1907, **40**, 1758, 3704; 1908, **41**, 850, 2860; Fischer and Königs, *Ber.*, 1907, **40**, 2048; Fischer and Schulze, *ibid.*, 943; Fischer and Gerngross, *Ber.*, 1909, **42**, 1485; Fischer and Luniak, *ibid.*, 4752. Fischer's papers have been reprinted in his book *Die Aminosäuren, Polypeptide und Proteine* (1906).

weight of at least 15,000, according to the results of the freezing-point method.*

There are two general methods of investigating the constitution of any given substance. In the one method we study the general properties of the substance ; then ask how a molecule can be synthesized whose reactions will resemble those of the one we are examining ; and finally having synthesized this body we compare its reactions with those of the original. In the analytical method, the molecule is taken to pieces in various ways ; a series of decomposition products is obtained ; and from which we endeavour to guess the manner in which they were arranged in the original molecule. Now, in the case of the albumins, the earlier researches were based upon the analytical method. This was to be foreseen, for it seemed almost impossible to build up molecules of such extreme complexity.

The oxidation of the albumins cannot be said to have yielded results of any great interest; the major part of our knowledge of these bodies has been obtained by means of hydrolysis reactions. When ferments are allowed to act upon protein derivatives, the bodies first formed are albumoses and peptones. These intermediate compounds can be further broken down into amino-acids. Hydrolysis by means of alkali takes place more rapidly, but acids decompose the albumins most easily. It is thus made clear that the substances lying at the base of the albumins belong to the class of amino-acids; and, further, that these acid nuclei are linked together in some way which allows them to be separated one from another by means of hydrolysis. It is evident that amide-formation is the most probable method of uniting the nuclei; and from this point of view Fischer took up the work of synthesizing some compounds which, while not themselves of the protein class, would show sufficient resemblance to the naturally occurring substances to allow us to deduce the probable constitution of at least part of the albumin molecule.

To describe these synthetic substances, Fischer proposed the name "*Polypeptides*," by which he meant to denote those compounds which are derived from two amino-acid molecules by the elimination of one molecule of water. A few polypeptides

* Owing to the colloidal nature of the albumins, it is unsafe to place too much reliance on the exactitude of these results.

have been obtained by the hydrolysis of proteins, but by far the greater number are synthetic.

2. *Methods of Synthesizing Polypeptides*

As a first step in polypeptide syntheses, it was necessary to obtain mono-amino-acids. This Fischer did by means of the ordinary methods—action of ammonia on the esters of bromo-fatty acids or by Strecker's cyanhydrin method (addition of hydrocyanic acid and ammonia to an aldehyde and hydrolysis of the cyanhydrin thus formed). Now, having obtained these acids, another problem presents itself. If we combine together two racemic acids we shall have not a single reaction product, but a mixture of two new racemic substances. For instance, if we start with racemic alanine and racemic leucine, we should produce a mixture of the four isomers—

d-Alanine-*d*-leucine.	*d*-Alanine-*l*-leucine.
l-Alanine-*l*-leucine.	*l*-Alanine-*d*-leucine.

The two substances in the left-hand column then combine to form a racemic substance, and the two in the right-hand column to form *another* racemic compound, so that we should have two new bodies instead of a pure compound. And, of course, if we coupled together more than two racemic acids we should find the number of stereo-isomers in the product increased in like manner. This evidently threw considerable difficulty in the way, and to avoid it Fischer resolved to use in his condensations optically active acids only. By this means he excluded the possibility of racemic compounds being formed, so that from one pair of amino-acids he obtained only a single reaction product.

This did not clear the experimental difficulties away, however; it only carried them one step further back. For, owing to the very weak acidity of the amino-acids, resolution of these substances into their optically active antipodes by salt-formation with active bases was by no means an easy task. Fischer evaded this difficulty in turn by one of his usual simple artifices. He benzoylated the amino-group of the acid, and thus reduced its basic properties to a minimum; thereafter, resolution into the optical antipodes presented no difficulty, and after this had been accomplished, the benzoyl radicle was split off and the optically active amino-acid remained.

I. The first method employed by Fischer in the actual synthesis of polypeptides depends upon the elimination of a molecule of alcohol from two molecules of amino-ester:

$$NH_2 . CH_2 . COOEt + NH_2 . CH_2 . COOEt$$
$$= NH_2 . CH_2 . CO . NH . CH_2 . COOEt + EtOH$$

Now, it will be seen at once that if this method be applied to a mixture of two different amino-acids, it would be sheer chance that would govern the production of the end-product. For example, if the two esters (A) and (B) react together we should probably get a mixture of (C), (D), (E), and (F), in the reaction product:

(A) $NH_2 . CH_2 . COOEt$

(B) $NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt$

(C) $NH_2 . CH_2 . CO . NH . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt$

(D) $NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CO . NH . CH_2 . COOEt$

(E) $NH_2 . CH_2 . CO . NH . CH_2COOEt$

(F) $NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CO . NH . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt$

This difficulty in its turn was overcome by Fischer in a very simple manner. Before condensing the two substances together he allowed one of them to react with ethyl chloroformate, which acted upon the amino-group and protected it from further attack:

$$Cl . COOEt + NH_2 . CH_2 . COOEt$$
$$= EtOOC . NH . CH_2 . COOEt + HCl$$

When a compound such as this is heated for thirty-six hours with the ester of an amino-acid, alcohol is eliminated between the $—NH_2$ group of the amino-acid and the $—CH_2 . COOEt$ group of the above substance, whose amino-group cannot react in this way. Thus the constitution of the resulting compound is determined. An example will serve to make the matter clear.

If we start with the substance glycyl-glycine,* and treat it with chloroformic ester, we shall obtain the substance shown below, glycyl-glycine carboxylic acid ester:

$$EtOOC\,.\,Cl + NH_2\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOEt$$
$$= EtOOC\,.\,NH\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOEt + HCl$$

When this substance is heated for thirty-six hours with leucine ester, ethyl alcohol is eliminated in the following way:—

$$EtOOC.NH.CH_2.CO.NH.CH_2.COOEt + NH_2.CH.(C_4H_9).COOEt$$
$$= EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH(C_4H_9)COOEt$$

This substance is the carboxylic ester of glycyl-glycyl-leucine; as can be seen from the formulæ, it can have no other constitution than that shown. This carbethoxy-glycylglycyl-leucine ester contains three amino-acid nuclei, and is therefore called a tri-peptide derivative.

II. The yields of end-product from the foregoing method of synthesis were poor, and Fischer therefore turned to another way of attaining his objective. When the ester of the chloroformic derivative of an amino-acid is treated with thionyl chloride, an acid chloride is formed; and this readily condenses with amino-esters, forming polypeptide derivatives. For instance, if we start again with the derivative obtained by the action of chloroformic ester upon glycylglycine, and treat it with thionyl chloride, we shall produce the chloride whose constitution is shown below:

$$EtOOC\,.\,NH\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,CO\,.\,Cl$$

When this chloride is condensed with glycylglycine ester:

$$NH_2\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOEt$$

it yields the tetra-peptide derivative, triglycylglycine-carbethoxy-ester:

$$EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.CO.NH.CH_2.COOEt$$

III. The drawback of the two foregoing methods lies in the fact that, so far, no method has been discovered for eliminating the group —COOEt, which is attached to one end of the polypeptide chain; so that neither method can be employed to build up a true polypeptide. Fischer therefore devised another method by means of which the polypeptides themselves can be

* Fischer terms "glycyl" the radicle $NH_2\,.\,CH_2\,.\,CO$— which is derived from glycine (glycocoll) $NH_2\,.\,CH_2\,.\,COOH$.

produced. Starting from the ester of a substance like glycine (I.) or glycylglycine, he treated this with chloracetyl chloride (II.) or some similar compound. Hydrochloric acid is eliminated, and the two molecules combine together to form a compound with chlorine at one end of the chain (III.). The ester group at the other end of the chain is then hydrolyzed very carefully, and a chloro-acid produced (IV.), which, on treatment with ammonia, yields a true polypeptide (V.):

(I.) $NH_2 . CH_2 . COOEt$
(II.) $Cl . CH_2 . CO . Cl$
(III.) $Cl . CH_2 . CO . NH . CH_2 . COOEt$
(IV.) $Cl . CH_2 . CO . NH . CH_2 . COOH$
(V.) $NH_2 . CH_2 . CO . NH . CH_2 . COOH$

The reason for hydrolyzing the ester (III.) to the acid (IV.), lies in the fact that, if this were not done, an amide would be formed on treatment with ammonia, and the amido-group would be most difficult to get rid of later.

IV. A variation of the previous method may also be used. If the substance:

$$Cl . CH_2 . CO . NH . CH_2 . COOH$$

which was formed in the course of the last synthesis we described, be treated with pentachloride of phosphorus, the acid is converted into the chloride: *

$$Cl . CH_2 . CO . NH . CH_2 CO . Cl$$

which can then be made to interact with glycine ester, yielding the more complicated substance:

$$Cl . CH_2 . CO . NH . CH_2 . CO . NH . CH_2 COOEt$$

The remaining chlorine atom may then be replaced by the amino-group by means of ammonia; and after hydrolysis of the ester group the tri-peptide glycyl-glycyl-glycine is formed:

$$NH_2 . CH_2 . CO . NH . CH_2 . CO . NH . CH_2 . COOH$$

V. This modification has been further extended. When amino-acids are treated with a mixture of acetyl chloride and

* Thionyl chloride is a better reagent than phosphorus pentachloride for producing acid chlorides. The reaction takes place according to the equation:

$$R . COOH + SOCl_2 = R . CO . Cl + SO_2 + HCl$$

from which it will be clear that the acid chloride can be obtained pure simply by boiling off the sulphur dioxide and hydrochloric acid.

phosphorus pentachloride, the corresponding acid chlorides are formed. These can be combined with other amino-acids, and in this way polypeptides can be obtained. For instance, if glycine be thus treated the product is glycyl chloride :

$$NH_2 . CH_2 . COOH \rightarrow NH_2 . CH_2 . CO . Cl$$

This can be condensed with another molecule of glycine, forming glycylglycine :

$$NH_2 . CH_2 . CO . Cl + NH_2 . CH_2 . COOH$$
$$= NH_2 . CH_2 . CO . NH . CH_2 . COOH$$

VI. If two molecules of alcohol be abstracted from two molecules of an α-amino-ester, a cyclic substance is produced, which is a derivative of $\alpha\gamma$-diketo-piperazine :

$$\begin{array}{l} CH_2\text{—}NH_2 \\ | \\ CO\text{—}OEt \end{array} + \begin{array}{r} EtO\text{—}CO \\ | \\ H_2N\text{—}CH_2 \end{array} = \begin{array}{l} CH_2\text{—}NH\text{—}CO \\ | \qquad\qquad\quad | \\ CO\text{—}NH\text{—}CH_2 \end{array} + 2EtOH$$

This cyclic compound, when carefully treated with hydrochloric acid, can be opened out into an open-chain body. glycylglycine :

$$\begin{array}{l} CH_2\text{—}NH\text{—}CO \\ | \qquad\qquad\quad | \\ CO\text{—}NH\text{—}CH_2 \end{array} + H_2O = \begin{array}{l} CH_2\text{—}NH_2 \quad COOH \\ | \qquad\qquad\quad\;\; | \\ CO\text{—}NH\text{——}CH_2 \end{array}$$

By choosing the appropriate amino-ester from which to start, a given polypeptide may be obtained in this manner.

It is not necessary in this place to go into details with regard to the various substances which have been synthesized by means of the foregoing methods, but there is one compound which is worthy of mention. Fischer eventually synthesized an octadecapeptide in the following manner. Starting from dextro-α-bromo-isocapronyl-diglycylglycine :

$$\begin{array}{l} Br . CH . CO . (NH . CH_2 . CO)_2 . NH . CH_2 . COOH \\ \qquad\; | \\ \qquad C_4H_9 \end{array}$$

he treated this according to the fourth method, combining it with penta-glycylglycine, and, finally, exchanging the bromine atom for an amino-group, he obtained lævo-leucyl-octaglycylglycine :

$$\begin{array}{l} NH_2 . CH . CO . (NH . CH_2 . CO)_8 . NH . CH_2 . COOH \\ \qquad\quad\;\; | \\ \qquad\;\; C_4H_9 \end{array}$$

This polypeptide was then coupled with dextro-bromo-isocaproyl-diglycylglycine, and again treated with ammonia, whereby the tetradecapeptide shown below was formed :

$$\underset{\displaystyle C_4H_9}{NH_2.\underset{|}{CH}}.CO(NH.CH_2.CO)_3.NH.\underset{\underset{\displaystyle C_4H_9}{|}}{CH}.CO.(NH.CH_2.CO)_8.NH.CH_2.COOH$$

Lævo-leucyl-triglycyl-lævo-leucyl-octaglycyl-glycine.

By a repetition of this series of reactions the octadecapeptide was formed, which has the constitution shown below :

$$NH_2.CH(C_4H_9).CO.(NH.CH_2.CO)_3.NH.CH(C_4H_9).CO.(NH.CH_2.CO)_3\,.\,NH.$$
$$|$$
$$HOOC.CH_2.NH.(CO.CH_2.NH)_8.CO.CH.C_4H_9$$

l-Leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine.

This substance is one of the most complicated systems of known constitution which has hitherto been synthesized. Its molecular weight is 1213, while that of the fairly complicated natural body, tri-stearin, is only 891.

3. *The Resemblances between the Polypeptides and the Proteins*

The main characteristics of the polypeptide class may now briefly be summarized, and it is of interest to compare them with those of the naturally occurring proteins. The polypeptides are solids, which usually melt at about 200° C., with some decomposition. They are easily soluble in water, but insoluble in alcohol, like some of the albumins ; and instead of having the usual insipid or sweet taste of the ordinary amino-acid, they are bitter, like the protein derivatives. In dilute sulphuric acid solution they are precipitated by phosphotungstic acid, in which behaviour they resemble the albumins. Both the natural and artificial classes give the biuret reaction. The action of ferments, or of acids or alkalis, is the same in both classes ; and similar products are obtained when animals are fed with polypeptides and albumins. In the case of ferment action it is found that much depends upon the groups which have been used in building up the polypeptide structure, some polypeptides being much more easily fermented than others.

4. *The Proteins*

In order to see the results of the polypeptide investigations in their true perspective, it is necessary to glance briefly at the

chemistry of the proteins. No attempt will be made to enter into the subject in detail, as it belongs to bio-chemistry rather than to pure organic chemistry; and the description of the properties of many ill-defined classes of compounds would merely prove wearisome without adding much to the information of the reader.

The proteins are nitrogenous materials which comprise the most important portion of the contents of cells in the animal body and which also occur in plants. They form the main constituents of animal nourishment and are thus converted into the substances from which the organized part of the animal frame is constructed. It is evident that they are of the greatest importance in vital processes.

The chemical investigation of this group of substances is beset with many difficulties, some of which are due to the colloidal nature of many proteins, while others arise from the complexity of the protein structure. Even the classification of the proteins is of the roughest nature, depending upon their solubility in various reagents and similar characteristics. Thus it is very difficult to decide, in some cases, whether a protein should be placed in one class or another; and this must be borne in mind lest the nomenclature should lead the reader to imagine that there is as sharp a distinction between, say, an albumin and a globulin as there is between an aliphatic acid and an aromatic alcohol.

The albumins, of which white of egg is a common example, are proteins soluble in water, from which they can be separated again by salting out. On heating, they undergo coagulation.

The globulins, on the other hand, are almost insoluble in water, but dissolve in dilute acids, alkalis, or salt solutions. They are coagulated on heating, and are precipitated by saturated solutions of magnesium sulphate, in which respect they resemble the albumins.

The sclero-proteins, such as gelatine and keratine, are distinguished by the fact that they form sticky, gelatinous materials when treated with water. They are also characterized by the readiness with which they dissolve in alcohol.

Allied to the foregoing are the protamines and histones, which are of a much simpler nature than the members of the first three classes. Of the two, the protamines are the more basic

in character; while the histones stand midway between them and the albumins in this respect. Both classes are found in fish sperm, generally combined with nucleic acid.

The next group of compounds is more complex in certain ways; for in addition to the ordinary type of albumin structure they contain other groups of a different nature, and they are therefore to be regarded as conjugated proteins.

The conjugated proteins may be divided into three classes according to the "prosthetic group" which they contain. In the case of those substances which contain nucleic acids, the class is termed nucleo-proteins; when a carbohydrate group is present, the compound belongs to the gluco-proteins; whilst if the prosthetic group be chromatogen, the body belongs to the chromo-protein series. Logically, the phospho-proteins and the lecitho-proteins ought also to be included under the heading of conjugated proteins.

Turning now to derivatives of the proteins and treating them in a descending order of complexity, the first class includes the meta-proteins. These are obtained by treating complex proteins with acid, which gives rise to acid-albumins, or with alkali, which yields alkali-albumins. The acid-albumins are insoluble in water or salt solutions, but soluble in dilute hydrochloric acid or sodium carbonate solutions. The alkali-albumins are insoluble in water or salt solutions. The main difference between the two classes is that the acid-albumins have no effect upon calcium carbonate, whereas the alkali-albumins liberate carbon dioxide from it.

The next class of protein derivatives contains the proteoses such as albumose, globulose, etc. These substances can be obtained from the albumins by hydrolytic decomposition in presence of certain enzymes. They are soluble in water even when their parent substances were insoluble; and the further the decomposition has proceeded, the more readily soluble the product appears to be. They can be salted out of solution by means of ammonium sulphate in presence of acetic acid.

Closely allied to the proteoses are the peptones, the main difference between the two classes being that the peptones are not thrown out of solution in presence of ammonium sulphate.

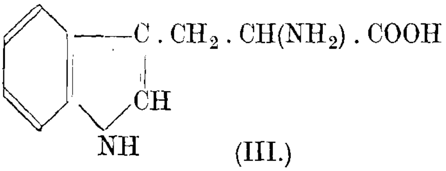
Finally, when the fission of the protein molecule has been

carried to its furthest stages, the polypeptides and the simple amino-acids are reached.

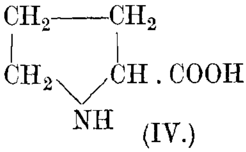
It must not be supposed that the foregoing simplified scheme includes all the degradation products of protein molecules. In addition to amino-acids, certain hydroxy-amino-acids and simple fatty acids have been isolated ; while sulphur derivatives such as cysteine (I.) and its oxidation product cystine (II.) are found. Tryptophane (III.) and proline (IV.) have also been recognized in some cases.

$HS \,.\, CH_2 \,.\, CH(NH_2) \,.\, COOH$ (I.)

$[S \,.\, CH_2 \,.\, CH(NH_2) \,.\, COOH]_2$ (II.)



(III.)



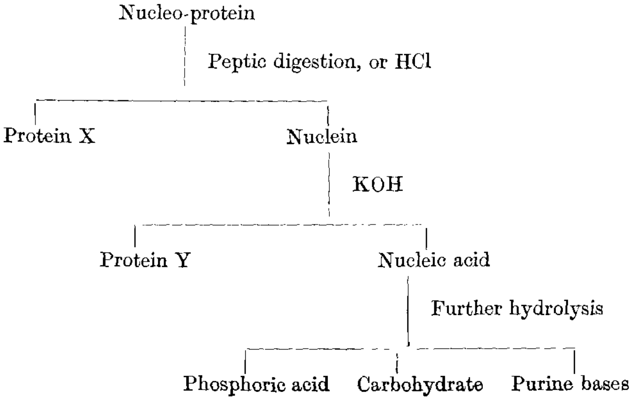
(IV.)

Carbohydrate derivatives have been detected, including a nitrogenous compound glucosamine :

$$CH_2OH \,.\, CH(OH) \,.\, CH(OH) \,.\, CH(OH) \,.\, CH(NH_2) \,.\, CHO$$

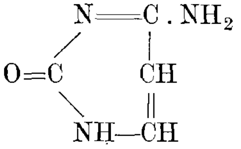
and the action of putrefying bacteria results in the formation of the diamines : putrescine $NH_2 \,.\, (CH_2)_4 \,.\, NH_2$, and cadaverine $NH_2 \,.\, (CH_2)_5 \,.\, NH_2$.

When a nucleo-protein is subjected to reagents which break it down the process is a complex one :

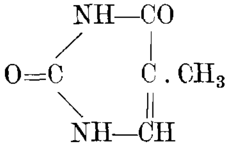


From this scheme it can be seen that when a nucleo-protein is acted on by pepsin or is hydrolyzed by means of dilute hydrochloric acid, it breaks down into two portions, one of which is a protein and the other a nuclein. Further hydrolysis decomposes the nuclein with the liberation of a second portion of protein, which may be different in constitution from the protein obtained in the previous hydrolysis; while a nucleic acid forms the remainder of the fission-products. Further decomposition of the nucleic acid yields various molecules belonging to the carbohydrate and purine groups and also phosphoric acid.

The constitution of the nucleic acids is not yet definitely established; but in the case of nucleic acid derived from the thymus gland the following decomposition products have been isolated: phosphoric acid, a hexose, two purine derivatives (guanine and adenine), and two pyrimidine derivatives (cytosine and thymine). Guanine is 2-amino-6-oxy-purine and adenine is 6-amino-purine. Cytosine and thymine have the structures shown below:

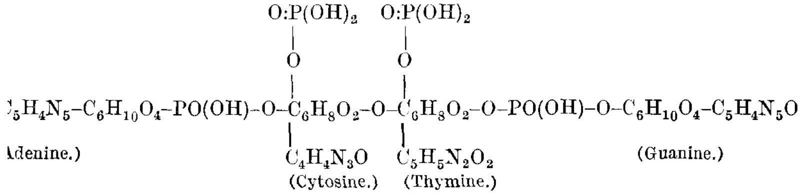


Cytosine.



Thymine.

It has been tentatively suggested that thymus nucleic acid has the following structure [1]; but it must be regarded as merely a probable conjecture and not as an established view.



The foregoing sketch is sufficient to show the extreme complexity of the protein structure; and it indicates in no uncertain way how far we still have to travel before we are able to make a definite statement with regard to the constitution of even the simplest member of the protein class. At the present time,

[1] Levene and Jacobs, *J. Biol. Chem.*, 1912, **12**, 377.

the upper limit of laboratory syntheses is reached with comparatively simple polypeptides ; but above that lie the peptones, proteoses and meta-proteins, all increasing in complexity ; and then come the proteins proper. Nor is this all ; for we have still to clear up the constitutions of the conjugated proteins with their nucleic acid, carbohydrate or chromatogen groups.

It will be seen that the problem of the cellulose constitution is a mere elementary exercise when compared with the complexity of the protein molecule ; for in the case of celluloses we have to deal with only the three elements carbon, hydrogen, oxygen ; and the decomposition products involved in the reactions of the compound are almost entirely confined to the sugar group : whereas in the proteins the introduction of the extra elements nitrogen and sulphur complicates the riddle, owing to the possible existence of many further types of linkage between the atoms.

CHAPTER XIV

TRIVALENT CARBON [1]

1. *Triphenylmethyl*

ANYONE who glances through the journals of the chemical world for the last twenty years must be struck by the enormous production of new compounds which has been and is at present going on ; and, if he reflects at all, he will be driven to ask himself what criterion should be applied in order to distinguish the really important substances from what may be termed the by-products of synthetic chemistry. Clearly the only fate which can overtake the majority of these new compounds is that their dossiers will be " neatly tucked away in Beilstein, the Abstracts published by the various Chemical Societies, or in other equally convenient depositories of information." They will remain at best in a dormant condition, waiting the time when some *Analogie-arbeit* necessitates a knowledge of their properties. On the other hand, those new bodies which have any interest apart from their melting-points soon become centres of new research ; and the more important of them usually lead to investigations extending far beyond the constitution and properties of the original compound. For example, the researches which more than a generation ago took their rise in the constitution of acetoacetic ester have not yet reached their final stages.

This ramification of interest has seldom been so strongly marked as in the case of the substance termed triphenylmethyl ; and it is the rapid extension of the field of research in this division of the subject which makes any treatment of the triphenylmethyl problem difficult. In the present chapter, it will be necessary to confine ourselves as far as possible to the narrow question

[1] For a general review of this subject, see Gomberg, *Chemical Reviews*, 1924, **1**, 91. Also Schmidlin, *Das Triphenylmethyl* (1914), and Walden, *Chemie d. freien Radikale* (1924).

of the constitution of triphenylmethyl and only to touch lightly upon the wider questions which are closely bound up with it.

The discovery of triphenylmethyl resulted from an attempt to prepare hexaphenyl-ethane, which was made by Gomberg [1] in 1900. He allowed "molecular" silver to act upon triphenyl-bromo-methane, and obtained a compound which he naturally supposed to be hexaphenyl-ethane; for the reaction would normally have taken the course expressed in the formulæ below:

$$2\,(C_6H_5)_3C.Br + 2\,Ag = (C_6H_5)_3C{-}C(C_6H_5)_3 + 2\,AgBr$$

On analysis, however, the substance was found to have about 6 per cent. too little carbon to agree with the hexaphenyl-ethane formula; and further examination showed that it could not be a hydrocarbon at all, but must contain oxygen.

This oxygen might have been introduced in either of two ways: it might have been imported through the silver used in the reaction; or it might have been derived from the air. The experiments were therefore repeated, other metals (such as zinc and mercury) being used instead of silver; and still the resulting substance was found to be oxygenated. From this it was clear that atmospheric oxygen was the source of the oxygen in the end-product; and further experiments were made in which precautions were taken to exclude air from the apparatus. The end-product in this case differed from that which had previously been obtained; and on analysis it was found to have the composition corresponding to hexaphenyl-ethane.

An examination of its properties, however, brought Gomberg to the conclusion that the substance which he had obtained could not be hexaphenyl-ethane; for he had expected that that body would be an extremely stable compound, whereas his synthetic hydrocarbon was very reactive.

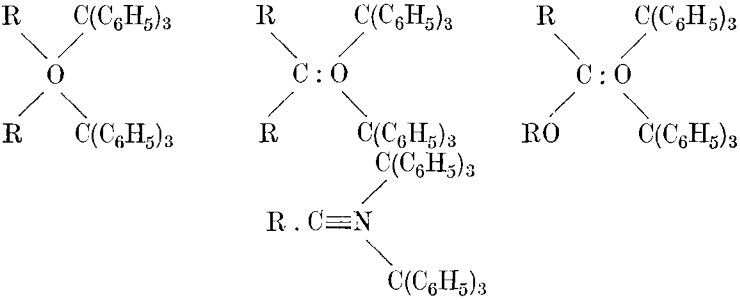
At this point a *résumé* of the chief properties of the hydrocarbon may be given. When first prepared, it is a colourless crystalline solid, which dissolves with great readiness in most organic solvents, giving yellow solutions. Even at zero it reacts with iodine to form triphenylmethyl iodide. Exposure to the air even for a short time is sufficient to transform it into a peroxide; and Gomberg [2] has proved that this same per-

[1] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.
[2] Gomberg, *Ber.*, 1900, **33**, 3150.

oxide can be produced by the action of sodium peroxide on triphenyl-chloro-methane (but not by the spontaneous oxidation of triphenylmethyl chloride or of triphenyl-carbinol under the same conditions). From this it may be inferred that the peroxide has the constitution:

$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

The hydrocarbon forms double compounds [1] with ethers, esters, ketones, nitriles, or aromatic hydrocarbons (and amylene), the composition of these substances corresponding to one molecule of ether (or of the other substances) plus one molecule of hexaphenyl-ethane. Gomberg ascribed the formation of the oxygenated derivatives to the change of the oxygen from the divalent to the quadrivalent condition, and formulated the constitution of the substances generally as derivatives of the following types:—



The fact that these substances are actually compounds, and not simply mixtures in which the ether or other body is held mechanically, is proved by the fact that similar compounds are formed with carbon disulphide and chloroform; and these latter bodies can be heated to 110° C. in a stream of carbon dioxide without giving up their full content of chloroform or disulphide. With sodium, the hydrocarbon forms a brick-red compound [2] having the formula $(C_6H_5)_3C . Na$ which is very reactive.

There is one further point to which attention must be drawn, though it does not directly concern the hydrocarbon. It has

[1] Gomberg, *Ber.*, 1905, **38**, 1333, 2447.
[2] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.

been shown[1] that the halogen salts, such as triphenylmethyl chloride $(C_6H_5)_3C.Cl$, and triphenylmethyl bromide $(C_6H_5)_3C.Br$, when dissolved in solvents such as liquid sulphur dioxide which have strong dissociating power, have conductivities very nearly equal to that of methylamine hydrochloride. This proves that in the yellow solutions obtained in this way, the compounds are split up into two ions, one of which must be $(C_6H_5)_3C$.

From the data given in the preceding paragraphs, it is clear that the problem of the constitution of Gomberg's synthetic hydrocarbon opened up a wide field for speculation; and numerous attempts were made to discover the solution. Four views have at one time or another gained a certain amount of support, and these will be described in the following sections.

2. *The Trivalent Carbon Hypothesis*

The reactions of his synthetic hydrocarbon—which we may for the sake of convenience term triphenylmethyl—led Gomberg[2] to put forward the view that the substance contained one carbon atom attached to three phenyl radicles, but having no fourth radicle attached to it:—

$$\left.\begin{array}{l} C_6H_5 \\ C_6H_5 \\ C_6H_5 \end{array}\right> C$$

The fourth valency of the carbon atom may be supposed to be free, or to be absorbed by the residual valency of the three phenyl groups. This conception of a trivalent carbon atom is really not so extraordinary as it seems; for we might consider that ethylene derivatives contain two adjacent carbon atoms of this type, instead of writing their structural formulæ as we usually do with a double bond between the two unsaturated carbons.

In favour of this constitutional formula for triphenylmethyl we may urge the evidence derived from the reactions of the substance with iodine and with oxygen, both of which can be expressed quite simply:—

$$\begin{array}{ccccc} (C_6H_5)_3C & & I & & (C_6H_5)_3C\,.\,I \\ & + & | & = & \\ (C_6H_5)_3C & & I & & (C_6H_5)_3C\,.\,I \end{array}$$

[1] Walden, *Ber.*, 1902, **35**, 2018; Gomberg, *ibid.*, 2045. Compare Gomberg, *Ber.*, 1905, **38**, 1342.

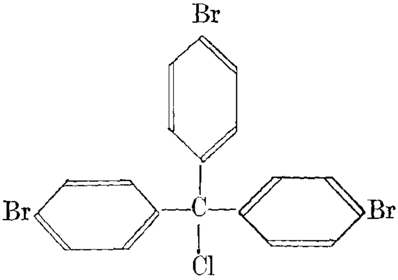
[2] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

$$\begin{array}{lcl} (C_6H_5)_3C & \ O & (C_6H_5)_3C{-}O \\ & + \ \| \ = & \qquad\quad | \\ (C_6H_5)_3C & \ O & (C_6H_5)_3C{-}O \end{array}$$

And we might also adduce the simplicity of the formulæ for the double compounds of triphenylmethyl with ethers, ketones, nitriles, etc.

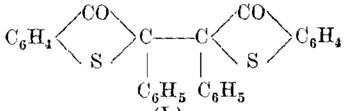
All that this amounts to, however, is that these reactions can be expressed in a straightforward manner on the assumption of trivalent carbon.* If they can be symbolized equally convincingly by means of a formula containing only quadrivalent atoms, then we should be entitled to reject the trivalent carbon view as adding an unnecessary assumption to our usual ones.

But there are facts which conflict with the trivalent carbon view. Gomberg and Cone [1] have shown that the three phenyl radicles do not possess identical properties, as they should do if the substance actually had the triphenylmethyl structure. We need only outline their proof here, as we shall have to return to it in a later section. By subjecting para-rosaniline to Sandmeyer's reaction they obtained tri-*p*-bromo-triphenyl carbinol, which, by the action of hydrochloric acid, was transformed into tri-*p*-bromo-triphenylmethyl chloride :

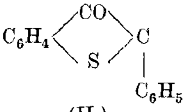


When this substance was treated in the usual way with silver, it gave a substance analogous to triphenylmethyl. This new

* Kalb and Bayer (*Ber.*, 1913, **46**, 3879) state that 2, 2′-diphenylthioindigo white (I.) dissociates in solution into two free radicles each containing trivalent carbon and having the structure (II.):

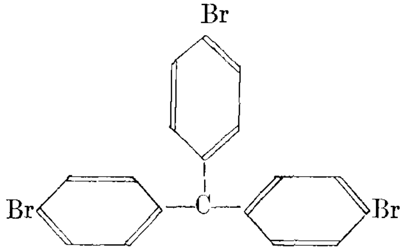


(I.)



(II.)

compound formed a peroxide just as triphenylmethyl does, and therefore (if the trivalent carbon idea be correct) we might safely assume that it is tri-*p*-bromo-triphenylmethyl :



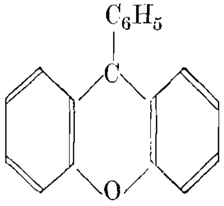
Now the tri-*p*-bromo-triphenyl chloride was sealed up in an air-free flask with excess of molecular silver, and the whole was shaken for a considerable time. At the end of this, it was found that the silver had removed all the chlorine (reaction of triphenylmethyl formation), but in addition it had abstracted one atom of bromine from the ring of one of the phenyl groups. Since there was excess of silver present, if all the three phenyl radicles had identical properties we should expect that they would yield up their bromine simultaneously. Further, the new compound produced by the elimination of bromine was not a peroxide similar to that formed by triphenylmethyl, nor did it yield such a peroxide when exposed to air. The experiments were repeated with other halogen derivatives of triphenylmethyl, and led in these cases to similar results. It is thus shown : (1) That the substitution of three bromine atoms in the position para to the "trivalent" carbon of triphenylmethyl in no way interferes with the activity of the substance ; (2) further action of silver eliminates only one of the three bromine atoms, so that one nucleus differs from the other two. From (1) the complete analogy between triphenylmethyl and its tribromo-derivative is clear ; and hence we are entitled to draw the conclusion that the inference in (2) is valid also for the parent hydrocarbon. But if in triphenylmethyl there is one phenyl nucleus endowed with properties not shared by the other two, it is evident that a symmetrical formula—

$$\left.\begin{array}{l} C_6H_5 \\ C_6H_5 \\ C_6H_5 \end{array}\right> C$$

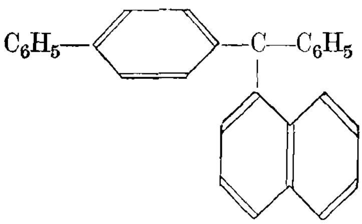
cannot give a true representation of the substance's properties.

A further complication is introduced into the problem by a consideration of the molecular weight of triphenylmethyl in solution. If the free radicle triphenylmethyl, $C_{19}H_{15}$, is present, then the molecular weight should be 243; whereas if hexaphenyl-ethane is formed, its molecular weight ought to be 486. Actual experiments show that in naphthalene at 80° C. the molecular weight is 414; whilst in benzene near 0° C. it appears to be 480–485.[1] These results suggest that under certain conditions the hexaphenyl-ethane dissociates to some extent into triphenylmethyl radicles.

This idea received further support from the work of Schlenk[2] on other compounds of the triphenylmethyl type. Thus the molecular weight of phenylxanthyl (I.) is 257 for the monomolecular (trivalent carbon) form and 514 for the bimolecular (quadrivalent carbon) substance. The actual value found in benzene by the ebullioscopic method is 279; pointing to the probability that 82 per cent. of the substance exists in the solution as a free radicle; whilst only 18 per cent. of the bimolecular form is present. Again, phenyl-biphenyl-*α*-naphthylmethyl (II.) should have a molecular weight of 369 for the free radicle and 738 for the bimolecular form. In boiling benzene the actual value determined was 362, which proves that the substance exists under these conditions as the free radicle.



(I.)



(II.)

[1] Gomberg and Cone, *Ber.*, 1904, **37**, 2037; 1906, **39**, 3274.
[2] Schlenk, *Annalen*, 1912, **394**, 178.

It was shown by Piccard [1] that the colour of triphenylmethyl solutions in ether deepened on dilution,* which suggests that the lowering of the concentration is accompanied by an increase in the dissociation of the bimolecular form; whilst Gomberg and Schoeffle [2] have studied the influence of the constitution of the triarylmethyls upon their degree of dissociation.

The foregoing evidence is thus somewhat confusing. On the one hand, it proves that triphenylmethyl cannot be symmetrical in structure; and on the other side it establishes the fact that the triarylmethyl derivatives do actually exist in solution in the form of free radicles. It is clear that we must seek further if we are to find a satisfactory solution of the problem.

3. *The Hexaphenyl-ethane Hypothesis*

When Gomberg's hydrocarbon was first prepared, its properties were found to be so different from what had been expected of hexaphenyl-ethane that the latter structure was at once dismissed as incapable of giving a proper representation of the reactions of the new substance; but as time went on, and more information with regard to the properties of the more highly phenylated ethanes was acquired, it seemed as if the earlier view had been rather hasty, and that there was a certain amount of probability in the idea that Gomberg's compound was, after all, merely hexaphenyl-ethane.

For two years, however, this view was kept in abeyance, owing to the fact that Ullmann and Borsum [3] had synthesized a substance which they regarded as hexaphenyl-ethane. This body was obtained by reducing triphenyl-carbinol; and its properties corresponded to some extent with those which had been anticipated for hexaphenyl-ethane. In 1904, however,

[1] Piccard, *Annalen*, 1911, **381**, 347; compare Hantzsch, *ibid.*, **384**, 135; 1913, **398**, 379.

* Normally, of course, dilution has no influence on absorption power since the light-ray passes through the same number of molecules in either concentrated or dilute solutions, provided that the thickness of the layer is kept directly proportional to the degree of dilution. This is known as Beer's Law.

[2] Gomberg and Schoeffle, *J. Amer. Chem. Soc.*, 1917, **39**, 1652.

[3] Ullmann and Borsum, *Ber.*, 1902, **25**, 2877; Gomberg, *ibid.*, 3914.

Tschitschibabin [1] established the constitution of this supposed hexaphenyl-ethane, proving it to be a compound of the following structure :—

$$(C_6H_5)_3C—C_6H_4—CH(C_6H_5)_2$$

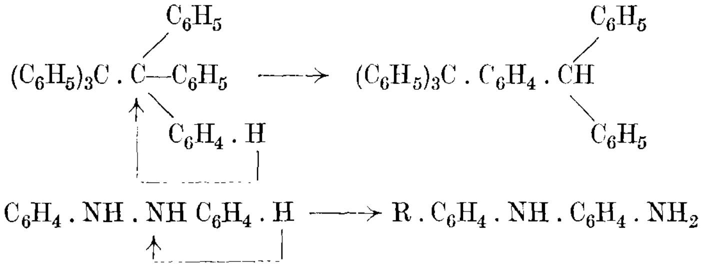
The removal of the supposed hexaphenyl-ethane from the literature thus left open the possibility that Gomberg's triphenylmethyl really had the hexaphenyl-ethane structure ; and Tschitschibabin put this suggestion forward, basing his views on the following considerations.

In the first place, we have to account for the reactivity of triphenylmethyl, and show why a compound of the hexaphenyl-ethane structure should be reactive. Tschitschibabin pointed out that an accumulation of electro-negative atoms or radicles in a molecule tends to make it much less stable. For example, Zincke showed that the accumulation of chlorine atoms in the phenol molecule leads to its degradation into simpler substances. Again, spatial factors sometimes come into play and cause a saturated substance like trimethylene to behave as if it were an unsaturated hydrocarbon. These considerations show that we must be prepared for certain anomalies and must beware of judging problems of constitution on too rigid lines. Further, it is not necessary to assume an unsaturated structure for triphenylmethyl merely in order to account for its ready reaction with oxygen to form a peroxide, for Gomberg [2] himself has shown that the fully saturated analogue triphenyl-iodomethane reacts in a similar manner. Nor is this all ; for when we examine more carefully the behaviour of the highly phenylated ethane derivatives we shall find that they are by no means so stable as analogy would lead us to expect. Tschitschibabin [3] has proved that even below its melting-point pentaphenyl-ethane is attacked by air ; at a temperature of only 150° C. hydrochloric acid in benzene solution acts on it so powerfully that the bond between the two ethane carbon atoms is broken, and such products as tetraphenyl-ethane, triphenyl-methane, and triphenyl-chloro-methane, are formed ; whilst Cone and Robinson [4] found that the action of phosphorus

[1] Tschitschibabin, *Ber.*, 1904, **37**, 4709.
[2] Gomberg, *Ber.*, 1902, **35**, 1836.
[3] Tschitschibabin, *Ber.*, 1907, **40**. 367.
[4] Cone and Robinson, *Ber.*, 1907, **40**, 2160.

pentachloride in boiling benzene broke down the pentaphenyl derivative into triphenylmethyl chloride.

Against the hexaphenyl-ethane hypothesis we may adduce several arguments. In the first place, triphenylmethyl is a colourless solid, but its solutions are deep yellow in tint: no ordinary benzenoid derivative is known which behaves in this way. Stronger evidence is to be found in the work of Gomberg (mentioned in the previous section), by which he showed that one phenyl group had properties different from those of the others. The ordinary hexaphenyl-ethane formula gives no indication of this. Thirdly, Gomberg [1] proved that his hydrocarbon can easily be converted into that which was obtained by Ullmann and Borsum. On the hexaphenyl-ethane hypothesis, this reaction would run the following course, which is parallel to that which is taken in the semidine change:



But Jacobson,[2] the greatest authority on the benzidine and semidine changes, regarded such a change in the triphenylmethyl series as most unlikely. Lastly, we have already seen that one of the most marked characteristics of triphenylmethyl is its capacity for forming double compounds with solvents; but no such property seems to be possessed by compounds analogous to hexaphenyl-ethane.

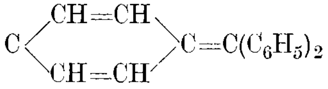
From the foregoing paragraphs, it is clear that most of the arguments both in favour of and against the hexaphenyl-ethane view depend to some extent upon analogy; and we must be careful not to lay too much stress upon them unless we are satisfied that the analogies really hold good. If we rule out the arguments based upon what a compound "ought" to do, it will be seen that the evidence remaining—Gomberg's dif-

[1] Gomberg, *Ber.*, 1902, **35**, 3918; 1903, **36**, 376.
[2] Jacobson, *Ber.*, 1904, **37**, 196.

ferentiation between the phenyl nuclei—tells against the hexaphenyl-ethane hypothesis.

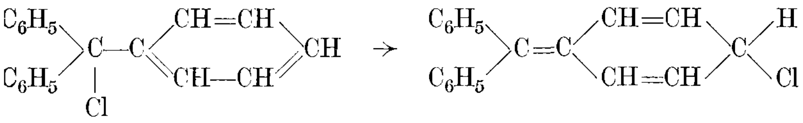
4. *Quinonoid Hypotheses*

If we reject the two hypotheses which were dealt with in the preceding sections, it is clear that we have still a third possibility open: for both the triphenylmethyl view and the hexaphenyl-ethane explanation were based on the assumption that the phenyl nuclei in triphenylmethyl were benzenoid in character; whereas by assuming a quinonoid structure for the substance we shall arrive at totally different types of formulæ. The quinonoid conception of triphenylmethyl was put forward very early in the compound's history by Kehrmann [1]—



This suggestion, involving as it does the assumption of a divalent carbon atom, meets with little approval at the present time; and since other formulæ of the quinonoid type have since been suggested which do not necessitate such a postulate, we need not deal further with this one.

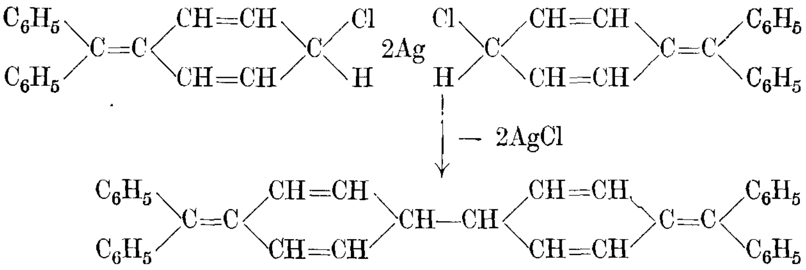
In 1903 Heintschel [2] put forward a new suggestion. On his hypothesis, the first step in the synthesis of triphenylmethyl is the conversion of triphenyl-chloro-methane into a desmotropic form in which the chlorine atom has been shifted into a position para to the methane carbon atom:



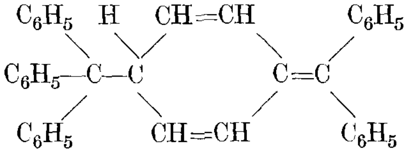
By the action of metals, two chlorine atoms are withdrawn from two molecules of the chloro-compound, and in this way triphenylmethyl is produced:

[1] Kehrmann, *Ber.*, 1901, **34**, 3818; see also Norris and Sanders, *Am. Chem. J.*, 1901, **25**, 117; and Gomberg, *Ber.*, 1902, **35**, 1824.

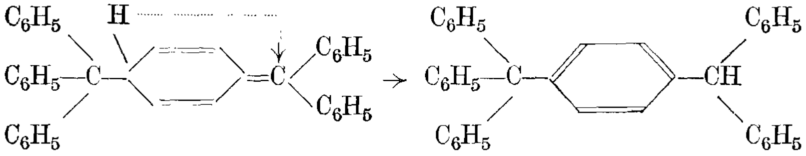
[2] Heintschel, *Ber.*, 1903, **36**, 320, 579.



An examination of Heintschel's formula will show that it contains two quinonoid phenyl nuclei. Jacobson [1] proposed to modify this, making only one phenyl group quinonoid, as shown below :



This view makes triphenylmethyl a derivative of a substance approaching the quinole type ; and as the reactivity of the quinoles is quite abnormal, we might expect considerable reactive power from a body having the structure proposed by Jacobson. The change of the Gomberg hydrocarbon into the substance prepared by Ullmann and Borsum can also be easily explained on this hypothesis, as the wandering of a single hydrogen atom is sufficient to account for the isomerization :



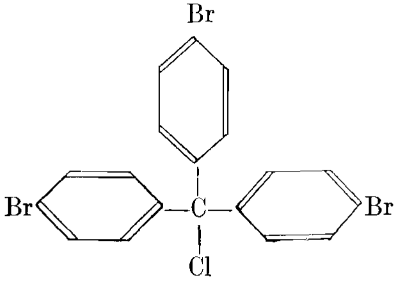
Gomberg's hydrocarbon. Ullmann and Borsum's hydrocarbon.

The Jacobson formula helps us to understand the fact that this substance, containing six phenyl radicles, can act as if it had the constitution of triphenylmethyl ; for if it be assumed that the molecule is decomposed by halogens in such a way that the single bond between the quinonoid nucleus and the adjacent carbon atom is loosened, then two " triphenylmethyl "

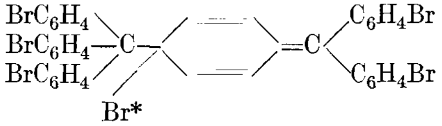
[1] Jacobson, *Ber.*, 1904, 37, 196.

radicles would be set free, which would at once react with halogen atoms giving two molecules of triphenylmethyl halide.

The quinonoid formula also makes clear the meaning of the experiments of Gomberg and Cone [1] to which reference was made in a previous section. Take for example the case of tri-*p*-bromotriphenylmethyl chloride :

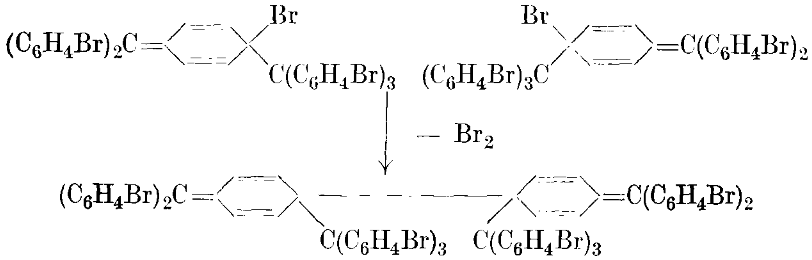


It is clear that, when it is converted into triphenylmethyl by the action of metals, one of the phenyl radicles must become quinonoid ; and an examination of the formula of the substance which would be formed if the quinonoid view be correct will show that one of the halogen atoms (marked with an asterisk) should possess the properties of a halogen atom attached to an aliphatic chain rather than those which are shown by halogen atoms bound to aromatic nuclei :



Now, such a halogen atom will be more easily attacked by metals than will be the case with the other bromine atoms in the compound in question ; so that we should expect that the action of an excess of, say, silver upon the tri-*p*-bromo-triphenylmethane chloride will result in two reactions, the first of which will lead to the elimination of two chlorine atoms, giving rise to the compound whose formula is shown above, while the further action of the silver will remove two bromine atoms from two molecules of this body, the result being the formation of a substance having the constitution shown below :

[1] Gomberg and Cone, *Ber.*, **1906, 39, 3274.**



The results obtained experimentally by Gomberg and Cone proved that one of the phenyl radicles did actually change from the benzenoid to the quinonoid form ; but in the view of these experimenters the assumption of this change alone was not sufficient to account fully for the problems which the properties of triphenylmethyl suggest.

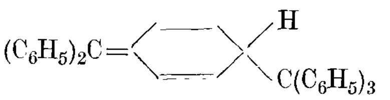
We must now turn to examine the objections which have been brought against the quinonoid view.

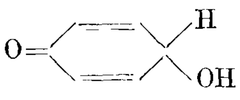
Tschitschibabin [1] pointed out that one of the most speedy and apparently simple reactions which the triphenylmethyl derivatives undergo is the formation of the peroxide :

$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

but to explain this according to the Jacobson formula we should have to assume an extremely complicated isomeric change as the first step in the process.

Gomberg and Cone [2] drew attention to the fact that Jacobson makes triphenylmethyl a derivative of a substance analogous to a secondary quinole :

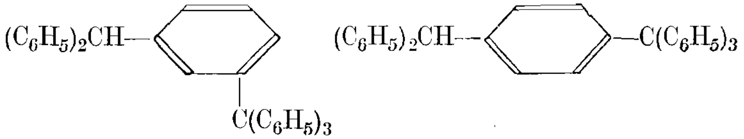




But since secondary quinoles have not yet been proved to be capable of existence, these authors considered doubtful the existence of compounds of the Jacobson type. Furthermore, if we grant the possibility of their existence, it is probable that they will behave like ordinary quinoles, and hence their reactions with acids should resemble to some extent the rearrangements which quinoles undergo under the same conditions. Now

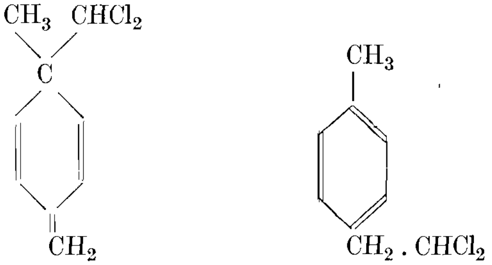
[1] Tschitschibabin, *Ber.*, 1905, **38**, 771.
[2] Gomberg and Cone, *Ber.*, 1906, **38**, 771.

in the quinoles, the alkyl group usually wanders to the ortho-position; whence by analogy the substance produced by the action of acids upon triphenylmethyl (Ullmann and Borsum's hydrocarbon) should be represented by the formula (I.) and not by (II.), though Tschitschibabin believed that (II.) was formed. These arguments, as the authors themselves admitted, are purely theoretical, and depend largely upon negative evidence.



(I.) (II.)

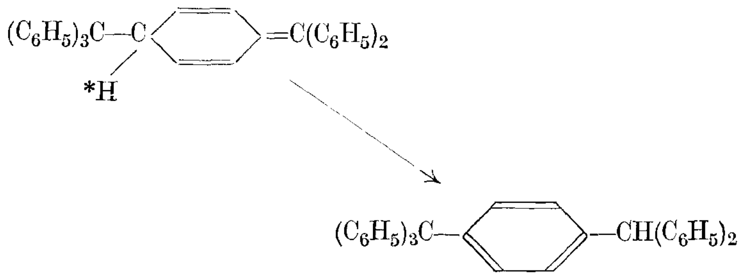
From a somewhat similar standpoint Auwers[1] criticized the Jacobson formula. He pointed out that the para-methylene quinonoid derivatives show such a tendency to revert to the benzenoid structure that in some cases a profound intramolecular change may take place. For example, in the compound (I.) below, the group —$CHCl_2$ wanders from its original position to the atom next the para-carbon atom in order to facilitate the formation of the benzenoid ring (II.) in preference to the quinonoid one:



(I.) (II.)

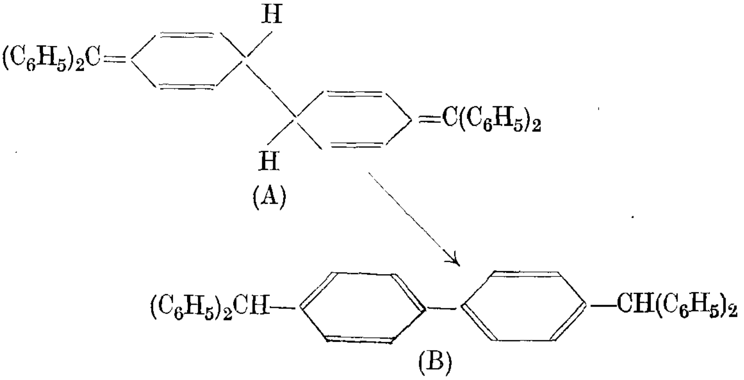
By analogy, it seems hardly likely that the hydrogen atom marked with an asterisk in the Jacobson formula would remain fixed in its present position when, by a similar wandering to the para-carbon atom, it could allow the compound to revert to the benzenoid type:

[1] Auwers, *Ber.*, 1907, **40**, 2159.



That such a wandering must be possible is shown by the conversion of the Jacobson compound into that of Ullmann and Borsum by the action of acids; but it seems strange that a compound of the Jacobson formula should exist in the free state at all.

Against the Heintschel formula (A), it has been alleged by Tschitschibabin[1] that it should be easily isomerized into a compound having the structure (B); whereas in practice no such change takes place:



From the foregoing summary it will be seen that the arguments both in favour of and against the quinonoid structure for triphenylmethyl are based very largely upon considerations of what a compound "ought" to do if it has a structure analogous to some other compound, the latter body being as yet undiscovered in practice. As far as the relevant evidence is concerned, it certainly goes to show that the quinonoid formula is a step in advance of either the triphenylmethyl hypothesis

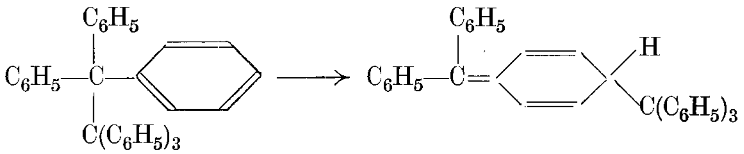
[1] Tschitschibabin, *Ber.*, 1905, **38**, 771.

or the hexaphenyl-ethane view, though it fails to account for the molecular weights established by Schlenk.

5. *The Tautomerism Hypothesis*

We have now exhausted the possibilities of static formulæ to explain the behaviour of triphenylmethyl; and it is evident that the results have not been completely satisfactory. All the three views discussed in the foregoing sections have certain advantages; and each has its own drawbacks. It thus becomes clear that, if any further progress towards a solution of the problem is to be made, we must contrive some means of uniting the advantages of the various formulæ; while at the same time we must endeavour to minimize their weak points. In order to do this it is obvious that we must turn to modern dynamic ideas and represent triphenylmethyl as a series of equilibrium mixtures of isomerides. Gomberg[1] has developed this line of thought; and if his results do not represent the truth, it seems probable that they come very close to it.

Gomberg's later views took their rise in the fact that there are two varieties of triphenylmethyl which differ from each other in colour: the solid form of the substance is colourless; but in solution this is changed into a yellow compound. Schmidlin[2] stated that he obtained the two forms of the substance in solution. Now, Gomberg assumed in the first place that there are two tautomeric forms of triphenylmethyl, $C_{38}H_{30}$; and in the second place that the radicle triphenylmethyl, $(C_6H_5)_3C$, can exist as such and is also capable of tautomerization. Let us now take up the possible constitution of the solid, colourless modification. This may be supposed to be hexaphenyl-ethane. It is evident that we may assume tautomeric change in this compound, leading to the following structure:—



This alteration of the benzenoid into the quinonoid form would

[1] Gomberg, *Ber.*, 1907, **40**, 1880.
[2] Schmidlin, *Ber.*, 1908, **41**, 2471.

be accompanied by a change of the substance from colourless to yellow; and since all ordinary solvents seem to be capable of yielding yellow solutions of triphenylmethyl, we may assume that this change from the benzenoid to the quinonoid form takes place under the action of most solvents during the process of solution.

We must now go a step further and deal with the behaviour of triphenylmethyl dissolved in a medium of high dissociating power, liquid sulphur dioxide. It has been proved by Walden [1] that a solution of the hydrocarbon in this solvent possesses a fairly high conductivity, and that the molecular conductivity increases with the dilution; in other words, the substance behaves just like an ordinary ionized salt. From this behaviour Gomberg inferred that tautomerization is not the only change which triphenylmethyl undergoes as it is dissolved; but that in addition it is dissociated [2] into two ions which we may represent as below. The anion is supposed to have the benzenoid structure, while the kation is quinonoid:

$$(C_6H_5)_2C : C_6H_4\begin{matrix} \diagup H \\ \diagdown C(C_6H_5)_3 \end{matrix} \quad \begin{matrix} \longleftarrow & \overset{\text{(Quinonoid)}}{\left[(C_6H_5)_2C : C_6H_4\begin{matrix} \diagup H \\ \diagdown \end{matrix}\right]^{+}} \\ \longrightarrow & \underset{\text{(Benzenoid)}}{\left[(C_6H_5)_3C\text{—}\right]^{-}} \end{matrix}$$

On this view the action of iodine upon triphenylmethyl solutions is explicable. The iodine in solution is supposed to interact with both the anion and the kation, yielding one molecule of benzenoid triphenylmethyl iodide and one molecule in the quinonoid form; but since the latter seems to be incapable of existence in the free state, it is assumed that it undergoes intramolecular change at once and produces a benzenoid molecule. When we turn to the action of oxygen upon triphenylmethyl in solution, however, we have a somewhat different state of affairs, since only the anion unites with oxygen. (This follows from the fact that the peroxide formed has the benzenoid structure, whereas the action of oxygen upon the quinonoid ion would give rise to a highly complicated substance which is not

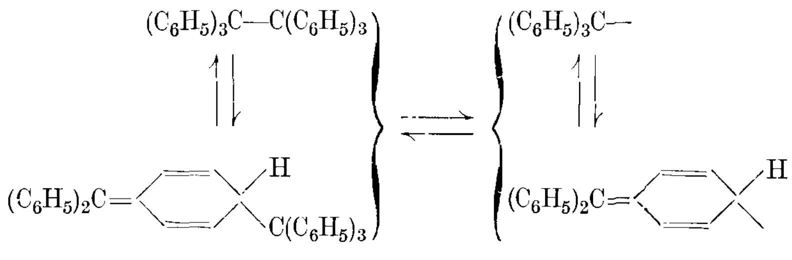
[1] Walden, *Zeit. phys. Chem.*, 1903, **43**, 443; Gomberg and Cone, *Ber.*, 1904, **37**, 2403.

[2] Compare De, *J.*, 1919, **115**, 127.

observed among the reaction products.) We are thus led to the further assumption that in the process of peroxide formation the first step is the oxidation of the benzenoid ions; as these are removed from the solution, equilibrium is disturbed; and, in order to re-establish it, some of the quinonoid ions must re-tautomerize into the benzenoid form. They in turn are removed by the oxygen; and the process continues until all the triphenylmethyl is exhausted.

The same tautomerization process can be invoked to explain why triphenylmethyl gives a yellow solution with ethers, esters, and ketones, while the solid double compounds which crystallize out from these solutions are colourless. In this case the benzenoid ions may be assumed to unite with the quadrivalent oxygen of the ethers, etc.; and in order to take their place some of the quinonoid ions are converted into benzenoid ones.

According to Gomberg,[1] then, all the important properties of triphenylmethyl can be explained on the basis of the following hypothesis: (1) tautomerization of hexaphenyl-ethane to a quinonoid substance having the Jacobson formula; (2) partial dissociation of this compound into positive and negative ions in all solvents; (3) mutual interconvertibility of these ions by tautomeric change; and (4) the existence of trivalent carbon atoms giving rise to free radicles. Thus a complete representation of triphenylmethyl's mutations is given by the following scheme:—



One final piece of evidence may be mentioned here, though its bearing upon the triphenylmethyl problem is an indirect one. If we discard the hypothesis of a quinonoid structure in triphenylmethyl, we are driven back to the idea that the

[1] Gomberg and Schoeffle, *J. Amer. Chem. Soc.*, 1917, **39**, 1652; Gomberg and Sullivan, *ibid.*, 1922, **44**, 1829.

three phenyl radicles, in view of their great amount of residual affinity, affect the fourth valency of the methyl carbon atom and thus allow its trivalence. But if this were so, then three other unsaturated radicles should have the same effect. Now tetranitromethane in certain solvents [1] shows a development of colour similar to that exhibited by triphenylmethyl; and it might be assumed that under these circumstances it was dissociated into a free nitro-group and trinitromethyl:

$$(NO_2)_3C . NO_2 \longrightarrow (NO_2)_3C— \quad + \quad —NO_2$$

The fact that the absorption band produced is independent of the nature of the solvent used [2] (provided that any colour is developed at all) seems to support this view.

To test this idea, a series of determinations of the molecular weight of tetranitromethane was carried out [3] in solvents yielding coloured solutions with the solute and also others in which no colour was developed. The method employed was the cryoscopic one. In no case was any sign of dissociation to be found. Solutions of tetranitromethane in acetic acid (where no colour is exhibited) and in naphthalene (which changes to the tint of azobenzene in presence of 2 per cent. of tetranitromethane) gave freezing-point depressions agreeing with the molecular weight of tetranitromethane within 0·2 per cent. Evidently no dissociation occurs in this case, although the three nitro-groups are quite as "negative" and unsaturated as the three phenyl radicles of triphenylmethane are. This seems to show that the explanation of the behaviour of triphenylmethyl must be sought in the nature of the phenyl radicles as distinct from their mere residual affinity.

6. *Cyclohexyl and Thiophenyl Derivatives containing Trivalent Carbon*

Conant and Sloan [4] devised a very simple method of obtaining trivalent carbon derivatives by the action of vanadous salts

[1] Ostromisslensky, *J. pr. Chem.*, 1911, **84**, 489; Clarke, Macbeth, and Stewart, *P.*, 1913, **29**, 161.

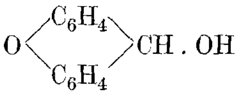
[2] Harper and Macbeth, *J.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824.

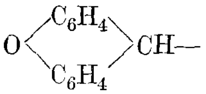
[3] Stewart, unpublished observation.

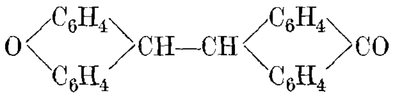
[4] Conant and Sloan, *J. Amer. Chem. Soc.*, 1923, **45**, 2466; 1925, **47**, 572; Conant, Small, and Taylor, *ibid.*, 1959.

upon certain carbinols and oxonium salts. For example, triphenyl-carbinol in hydrochloric acid solution is reduced to triphenylmethyl by vanadous chloride; and the same reagent converts triphenyl-pyrylium chloride into an unsaturated radicle.

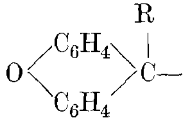
An application of this method in the case of xanthenol (I.) has resulted in the isolation of the corresponding free radicle (II.) in the solid state. When a very dilute solution of xanthenol in concentrated hydrochloric acid is treated with vanadous chloride, a pink precipitate is formed which can be filtered off and remains stable for some hours. It is gradually converted into colourless bixanthyl (III.):


(I.)


(II.)


(III.)

Conant and Small[1] have utilized this reaction in order to study the behaviour of a number of trivalent carbon derivatives with the structure:



in which the radicle R represents the following groups: *p*-chlorobenzyl; iso-amyl; *n*-hexyl; and cyclohexyl.

Gomberg and Jickling[2] extended the study of free radicles into the region of the heterocyclic compounds. From *a*-iodothiophene and benzophenone they prepared, by the Grignard reaction, thienyl-diphenyl carbinol; from which, by the action of hydrogen chloride, they obtained the corresponding chloride. When the last substance is treated in benzene solution with molecular silver or other metals, it exhibits a deep red colour

[1] Conant and Small, *J. Amer. Chem. Soc.*, 1925, **47**, 3068.
[2] Gomberg and Jickling, *J. Amer. Chem. Soc.*, 1913, **35**, 446.

and absorbs oxygen freely. The amount of oxygen absorbed indicates that the following reaction probably takes place :—

$$2\ \begin{matrix}C_4H_3S\\ C_6H_5\\ C_6H_5\end{matrix}\!\!>\!C \;+\; O_2 \;=\; \begin{matrix}C_4H_3S\\ C_6H_5\\ C_6H_5\end{matrix}\!\!>\!C{-}O{-}O{-}C\!<\!\!\begin{matrix}C_4H_3S\\ C_6H_5\\ C_6H_5\end{matrix}$$

thus bringing the new compound into line with triphenylmethyl in peroxide formation.

This opens up prospects of considerable interest; for the production or non-production of a trithienylmethyl would throw light upon the constitution of triphenylmethyl itself.

CHAPTER XV

UNSATURATION

1. *Types of Unsaturation*

When we examine the matter closely, it is found that the foundations of theoretical organic chemistry are a series of labels by means of which we endeavour to conceal our ignorance of the fundamental phenomena of the subject. Of these labels, none is used more indefinitely and at random than the word "Unsaturation." It seems not without some interest, therefore, to examine the various phenomena which are usually ascribed to the presence of this property, and to see if we can obtain some clear idea of what we mean by the word.

In the first place, let us ask ourselves what we mean by an unsaturated compound. The picture which is formed in our mind by these words usually represents two molecules uniting together, and one of these we are accustomed to call an unsaturated substance. But before going further a difficulty arises, for there seems no reason why we should consider one of the two molecules unsaturated and the other saturated. For example, if a molecule of bromine unites with a molecule of ethylene, we call ethylene an unsaturated hydrocarbon, but we do not regard the bromine molecule as unsaturated in the same sense. On closer examination, however, the difference between the two cases becomes clear. When ethylene takes up an atom of bromine the ethylene molecule is not completely disrupted; part of it remains as it was, for the two carbon atoms are still united, and each bears the same number of hydrogen atoms as before. With the bromine molecule, however, no trace of the original structure remains. Evidently our idea of an unsaturated compound must be extended; it is no longer sufficient to say that it is "a molecule capable of uniting with another

molecule"; but we must add, "without a disruption of its original structure." This definition covers practically every case which has any claims to be considered; and we may therefore adopt it and proceed to inquire if we can distinguish further between the various classes of substances which come within the definition.

The simplest type of an unsaturated compound with which we can deal is a component of a double salt. Here the amount of unsaturation is very slight, for the saturated body (double salt) may be decomposed into its components again by a mere change of temperature.

The second class of unsaturated compounds includes those in which the addition of new atoms takes place at one atom only, as, for example, trimethylamine, dimethyl-sulphide, dimethyl-pyrone, etc. In this case the least possible change in the general structure of the molecule takes place during the addition reaction.

The third class of unsaturated compounds contains those bodies which are capable of uniting with two atoms, but in which addition takes place at two adjacent atoms. The ethylene series, the ketones, and the nitriles are instances of this type.

There is another class of bodies which, while resembling the last-mentioned one, in so far as their capability of adding on only one pair of atoms is concerned, differs from it in the manner of addition; for, instead of the two incoming atoms attaching themselves to two adjacent atoms, as in the ethylene class, in this new series they attach themselves to non-adjacent carbon atoms. The polymethylenes furnish examples of this group.

Finally comes the acetylene class, in which we are able to unite four new atoms to two of the carbon atoms of the unsaturated compound.

Thus we have divided unsaturated bodies into the following five classes:—

1. Components of molecular compounds.
2. Compounds of monovalent iodine, divalent sulphur, selenium, tellurium, oxygen, etc., trivalent nitrogen, phosphorus, antimony, etc.
3. Compounds containing groups like C : C, C : N, C : O.
4. Cyclic compounds.
5. The acetylenes.

Of course, it is quite easy to multiply the possibilities by combining in one molecule representatives of each class, as in the case of mesityl oxide, for instance; but if we reduce the question to its simplest form, the above series will serve as a mode of classification.

Before entering into a consideration of these classes, however, we must deal with two other points which arise. What we call an unsaturated substance may be unsaturated with regard to one agent, and quite saturated towards another.[1] For instance, though all the substances in Class 3 are unsaturated with respect to nascent hydrogen, they differ in their behaviour towards bromine, ammonia, or water. Again, it is sometimes found that a compound may behave as a saturated or an unsaturated substance according to the conditions under which reactions are carried out. For example, in sunlight benzene forms addition products much more easily than in the dark. Thus there are fine differences for which we have no corresponding technical terms.

2. *The Effects of Unsaturation*

It would occupy too much space were we to enter into any detailed examination of the differences in physical properties between saturated substances and the unsaturated bodies from which they have been prepared. There is hardly a single physical property which remains common to the two groups. Melting-point, boiling-point, refractive index, optical rotatory power, absorption spectrum, magnetic rotation, crystalline form, electrical conductivity, and a host of other properties are all changed by the addition of as many atoms as the unsaturation requires.

The chemical effects of unsaturation are hardly less marked. Leaving out of consideration the chemical difference implied in the fact that the unsaturated compound is capable of adding on more atoms, while the saturated one is not, there are many other differences which the presence or absence of unsaturation in the molecule brings into view. For example, if we compare a saturated aliphatic acid with the corresponding unsaturated substance in which the double bond lies next the carboxyl

[1] See Vorländer, *Annalen*, 1902, **320**, 66.

group, the saturated acid will esterify with much greater ease than the unsaturated one.[1] Again, unsaturation may call into being a peculiar type of isomerism, of which the best example is found in the case of maleic and fumaric acids. Further, in the case of the acetylene series, the presence of unsaturation so alters the chemical characters of the hydrogen atoms that they become replaceable by metallic atoms; while, if acetylenic linkages are accumulated in a compound, it may become so unstable as to decompose with explosive violence. These few examples will suffice to illustrate the very varied influences exerted on the properties of compounds by unsaturation.

We may now turn to the question of the relative stability of various unsaturated compounds. In the first place, it is obvious that the amount of energy which is used up in saturating the component of a double salt cannot be very great; for if it were so, the double salt would not be decomposed again into its components with the ease which is found in practice. In the second class, saturated compounds are formed by calling into existence some latent affinities on the sulphur or nitrogen atoms. Now, these new salts—sulphonium, ammonium, phosphonium, or whatever they be—can, in many cases, be broken down into the unsaturated substance again by very simple means. For instance, merely by heating the quaternary ammonium salts we can obtain the amido-compounds from which we started. Thus, though we have here a set of substances more stable than the double salts, still the increase in stability is not very great. When we come to the groups 3, 4, and 5, the change from the saturated to the unsaturated body can only be brought about by chemical means, so that in their case we have passed into a new stage of the question.

There is another way of looking at the matter, and, for the sake of simplicity, we may confine our investigation in the rest of this chapter to the cases of the carbon compounds. If an ethylene derivative be compared with the isomeric polymethylene, we find that the former is much more readily attacked by reagents than the latter; in other words, the ethylene type is more unsaturated than the polymethylene. Thus, while ethylene compounds are almost instantaneously oxidized by permanganate,

[1] Sudborough and Roberts, *J.*, 1905, **87**, 1840; Sudborough and Thomas, *ibid.*, 1907, **91**, 1033.

the polymethylenes are not so rapidly destroyed. The acetylene series are even more sensitive to oxidizing agents than the ethylenes.

Now suppose that we have two isomeric substances, each capable of taking up four bromine atoms, are these two bodies equally saturated or are they not? The question of unsaturation thus resolves itself into one of stability. We cannot distinguish between the bodies by the *amount* of bromine they take up, so we seek some other criterion. Now, in the case of two substances, one of which has a pair of conjugated double bonds, while in the other the bonds are not so related, the second substance takes up the four bromine atoms at once, but the first one takes them up two by two. The action is thus more precipitate in the second instance, and we should be tempted to consider the first substance as the less unsaturated of the two. In fact, as Thiele put it, the conjugated double bonds partially saturate one another.

Further, when an unsaturated acid is brought into conditions which allow it to undergo isomeric change, it is almost always converted into the form which contains the ethylenic bond conjugated with that of the carboxyl group. Evidently, then, this grouping must be the most exothermic, and therefore the most saturated.

3. *Molecules with Two Centres of Unsaturation*

An interesting point arises when we combine in one molecule two different types of unsaturation, and then endeavour to find out which of them is the more readily saturated. For example, in mesityl oxide, we have in one molecule the double bond between two carbon atoms, and the other double bond between a carbon and an oxygen atom :—

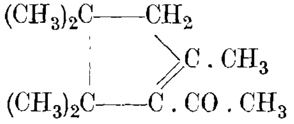
$$\begin{array}{r} (CH_3)_2C \\ \| \\ CH \\ | \\ CH_3\text{—}C \\ \| \\ O \end{array}$$

These two double bonds are of different types, and hence

some differences between their chemical activities might be expected. In the first place, of course, we find that the ethylenic bond will react with halogen acids, which do not attack the carbonyl group. But if we leave out of account such differences and confine ourselves to the action of those reagents which are capable of reacting with both linkages, the results are sufficiently striking. If mesityl oxide be reduced by means of weak alkaline reagents, such as sodium amalgam or aluminium amalgam, the carbonyl group remains intact, while the double bond is opened up. Two molecules of the ketone unite together to form a saturated diketone :

$$\begin{array}{l}(CH_3)_2C\,.\,CH_2\,.\,CO\,.\,CH_3\\ \quad\;\;|\\ (CH_3)_2C\,.\,CH_2\,.\,CO\,.\,CH_3\end{array}$$

(In the case of aliphatic ketones this diketone further condenses to a cyclic compound, in this instance desoxy-mesityl oxide—



while in the aromatic series the reaction may be stopped at the first stage.)

When sodium in aqueous ether is used as the reducing agent, the reaction takes quite a different course, for here both the carbonyl and the ethylene linkages are attacked simultaneously, giving the saturated alcohol :

$$(CH_3)_2CH\,.\,CH_2\,.\,CH(OH)\,.\,CH_3$$

No method has yet been discovered by which the carbonyl group of mesityl oxide can be reduced without destroying the ethylene linkage as well. But in the case of another ketone, such as :

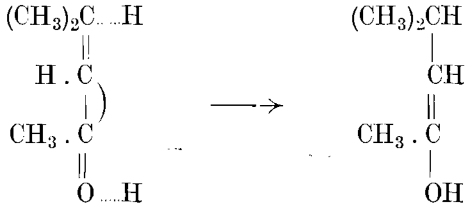
$$CH_2 : CH\,.\,CH_2\,.\,CO\,.\,CH_3$$

no difficulty whatever is found in reducing it with sodium in alcohol or aqueous ether to the unsaturated alcohol :

$$CH_2 : CH\,.\,CH_2\,.\,CH(OH)\,.\,CH_3$$

On comparing the structures of the two substances it is found that mesityl oxide contains a conjugated double bond, while in the second ketone there are two unconjugated linkages ;

thus in the case of mesityl oxide one bond cannot be attacked without tampering with the other, while in the second case we can reduce either separately. If we examine the mechanism of the reaction which is to be expected from Thiele's hypothesis in the case of mesityl oxide, we find that in the first place, hydrogen adds on to the two end partial valencies, as shown below :

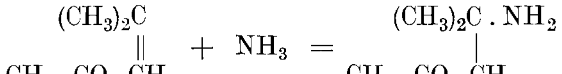


But this new body is merely the enolic form of the ketone :

$$(CH_3)_2CH \,.\, CH_2 \,.\, CO \,.\, CH_3$$

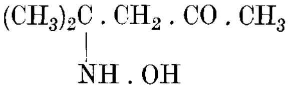
into which it will rearrange itself at once. Thus it is easy to understand why the carbonyl group is never reduced first when it is conjugated with another double bond of a different nature.

Again, ammonia is an agent which is capable of acting both upon carbonyl groups and on ethylenic linkages, but when it reacts with mesityl oxide it attacks only the double bond between the carbon atoms and leaves intact the carbonyl radicle :



Mesityl oxide. Diacetonamine.

The matter becomes a little clearer when we consider the action of hydroxylamine upon mesityl oxide.[1] If the action is allowed to take place in a methyl alcoholic solution in presence of sodium methylate, the chief product is the substance formed by the addition of hydroxylamine to the double bond :



[1] Harries and Lellmann, *Ber.*, 1897, **30**, 230, 2726 ; Harries and **Jablonski**, *ibid.*, 1898, **31**, 1371 ; Harries, *Annalen*, 1904, **330**, 181.

But if, on the other hand, hydroxylamine hydrochloride be exactly neutralized with sodium carbonate and then allowed to act upon an alcoholic solution of mesityl oxide, we get the usual carbonyl group reaction, and mesityl oxime is formed :

$$(CH_3)_2C : CH . C(NOH) . CH_3$$

Thus in *alkaline* solution the ethylenic bond is stimulated into activity, while in neutral solution the carbonyl radicle appears the more reactive of the two.

The influence of the conjugated double bond makes itself felt also in the cases of propenyl methyl and allyl methyl ketones. Blaise [1] examined these two isomeric substances, and found that when treated with one molecule of hydroxylamine in a neutral solution they are both converted into oximes :

$$CH_3 . CH : CH . CO . CH_3 \rightarrow CH_3 . CH : CH . C(NOH) . CH_3$$
$$CH_2 : CH . CH_2 . CO . CH_3 \rightarrow CH_2 : CH . CH_2 . C(NOH) . CH_3$$

But if they are treated with *two* molecules of hydroxylamine the results are different ; allyl methyl ketone reacts as in the last case, giving the oxime shown above, while propenyl methyl ketone reacts with two molecules of hydroxylamine to give the hydroxylamine-oxime derivative shown below :

$$\begin{array}{l} CH_3 . CH_2 \\ \qquad\quad | \\ \qquad\quad CH . NH . OH \\ \qquad\quad | \\ CH_3 . C : NOH \end{array}$$

Thus the conjugation of the ethylene and carbonyl bonds increases the activity of the ethylenic linkage in this case also. Blaise showed that exactly similar results were obtained with semicarbazide, the allyl ketone forming a semicarbazone, while the propenyl ketone, in virtue of its conjugated bonds, took up a second molecule of semicarbazide to form a semicarbazide-semicarbazone.

Posner [2] studied the matter very fully in order to find what effect various groups exert when placed near the ethylenic double bond. In the first place, he proved that the ethylenic linkage

[1] Blaise, *Bull. soc. chim.*, 1905, III. **33**, 42.

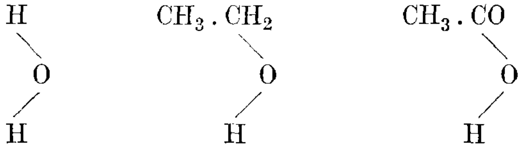
[2] Posner, *Ber.*, 1901, **34**, 1395 ; 1902, **35**, 799 ; 1903, **36**, 4305 ; 1905, **38**, 646 ; 1906, **39**, 3515 ; 1907, **40**, 218 ; Posner and Oppermann, *ibid.*, 1906, **39**, 3705.

alone was capable of taking up hydroxylamine and mercaptans, so that this addition-capacity does not depend entirely upon the proximity to the carbonyl group. When unsaturated acids were used, he found that the activity of the double bond was weakened if the carboxyl group was placed in its vicinity. Thus neither maleic nor fumaric acid could be induced to combine with hydroxylamine except to form the usual salts; iso-phenylcrotonic acid, on the other hand, in which the ethylene linkage is not conjugated with the double bond of a carboxyl group, takes up a hydroxylamine molecule with special ease. The $\alpha\beta$-unsaturated monocarboxylic acids gave with hydroxylamine α-oximino-acids, whilst $\alpha\beta$-unsaturated ketones form β-hydroxylamine derivatives.

Thus we cannot say definitely that the ethylenic linkage is more or less active than the carbonyl bond; for the matter is influenced in different ways by the reagent employed, the solvent used and the relative position of the two double bonds in the molecule. In other words, "unsaturation" is not a definite, measurable thing which we can predict in any case from the behaviour of the "unsaturated" substance in other circumstances; it is rather something kinetic, something which is extremely sensitive to external forces, and which in its turn can play a part in influencing the chemical action of groups which it does not apparently affect directly.

4. *The Vorländer Rule and Replaceable Hydrogen*

An interesting example of the effect of unsaturation upon chemical properties is to be found in the field which is covered by the Vorländer Rule.[1] Both acids and alcohols can be regarded as derivatives of water. Acetic acid may be looked upon as water with one hydrogen atom replaced by an acetyl radicle; whilst ethyl alcohol is simply a water molecule with an ethyl group instead of one hydrogen atom.



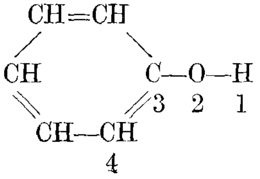
[1] Vorländer, *Ber.*, 1901, **34**, 1633.

On examining the chemical behaviour of the hydrogen atom in each case, we find that in the acids it has a much greater activity than in the alcohols. The origin of this difference obviously lies in the difference between the acyl and alkyl groups to which the hydroxyl radicle is united. The question is commonly dealt with by labelling the acyl group "electro-negative," and treating the label as an explanation. But, as Vorländer pointed out, this case is only one example of a general rule. If we represent non-metallic elements by E, and write down the following series :—

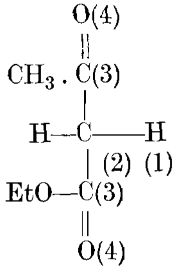
```
1 2 3 4
H . E . E : E

1 2 3
H . E : E

1 2 3 4 5
H . E . E . E : E
```

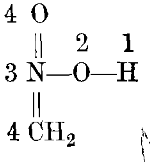
we shall find that the hydrogen atom in the first line has a greater reactivity than those in the second and third lines. In the first case the double bond between the two E atoms lies in the 3 : 4 position to the labile hydrogen atom, whereas, when the double bonds are in the 2 : 3 or 4 : 5 positions, the hydrogen is not specially active. For example, the labile hydrogen atoms in oximes, acids, phenols, diazo-compounds, and sulphinic acids are all situated as in the first type with respect to the double bond :

```
  4   3   2   1            4   3   2   1
R . CH : N . O . H         O : C . O . H
                               |
                               R

    4   3   2   1          4   3   2   1
   R—N : N . O . H         O : S . O . H
                               |
                               R
```

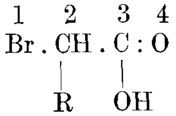


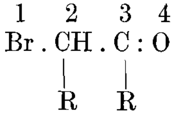
In acetoacetic ester and nitro-methane the hydrogen atoms are doubly influenced :



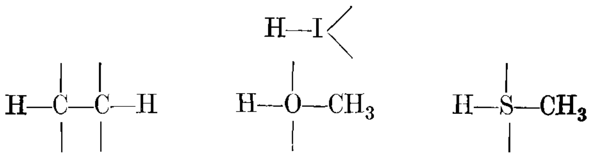


Further, when an acid or a ketone is brominated, the halogen atom enters the nucleus in the position required by this rule, *i.e.* it replaces the hydrogen atom in the α-position to the carbonyl group—

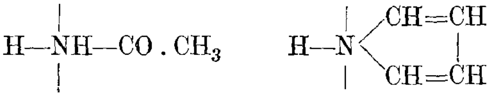




There seems to be another influence at work in the case of acidic hydrogen atoms ; and as the matter appears to have escaped notice hitherto, it may be well to call attention to it in this connection.[1] An examination of the formulæ of most substances which are capable of yielding metallic derivatives will show that the atom to which the labile hydrogen is attached is capable of exerting a valency higher than that which it exhibits in the acidic compound. For example, in the following substances the oxygen and sulphur atoms are divalent, while both oxygen and sulphur are capable of acting as quadrivalent elements ; carbon in acetylene acts as a divalent atom, though its maximum valency is four ; the nitrogen atoms shown below are trivalent, but nitrogen can act as a pentad ; iodine can act either as a mono- or a trivalent element. The formulæ are written with lines to show the extra valencies.



[1] Compare Smiles, *J.*, 1900, **77**, 160.



It will be seen that this is of more general application than the Vorländer Rule, for it holds in the case of substances such as ethylates, whose formation takes place though there is no double bond in the molecule such as is required by Vorländer's view.

5. *Summary*

We may now sum up, as far as possible, the various points which were treated in the foregoing pages. It is clear, in the first place, that unsaturation is not an intrinsic property of any molecule. It depends largely upon the nature of the outside reagent; in order to have "unsaturation" we must have two substances, each specially fitted to interact with the other. In fact, the addition reactions of organic chemistry appear to be an extreme case of the ordinary reactions of salt formation, such as takes place in the case of ammonia and acid. Secondly, the influence of the other (non-reacting) parts of the molecule may play a very considerable part in any addition reaction, so that we cannot ascribe the same meaning to every double bond that we write down. For example, the ethylenic bond in maleic acid must be chemically quite different from that in mesityl oxide. Thirdly, just as unsaturation can be influenced by neighbouring unsaturations, it can in turn exert an influence upon groups of atoms in its vicinity. And, finally, a series of unsaturations in a molecule can be made to rearrange themselves to form a more stable system.

From what has already been said, it is evident that the term "unsaturation" covers a very wide and ill-defined field. It seems possible that as the electronic ideas of G. N. Lewis become more generally applied to organic chemistry, we may gain some clearer views on the subject of unsaturated compounds; for his conceptions of firm and looser groupings of electrons seem peculiarly adapted to elucidate many of the problems which have been touched upon in the foregoing pages.

CHAPTER XVI

ORIENTING INFLUENCES IN THE BENZENE SYSTEM

1. *Introductory*

THE entry of substituents into the benzene system is certain to suggest to an organic chemist a number of problems which are not devoid of interest. In fact, so extensive is the material which has been collected on the subject, that only the merest outline can be given in the present chapter ; and fuller information must be sought in the books and papers which have been written to elucidate the matter.[1]

The introduction of fresh groups into the benzene nucleus may be either a direct or an indirect operation ; for example, chlorobenzene may be obtained by the direct action of chlorine upon benzene or else by applying the Sandmeyer reaction to aniline, whereby the chlorine atom replaces a substituent already present.

Confining attention for the present to the first of these processes, it seems worth while to inquire what substituent atoms or radicles can be attached to the benzene ring without the intermediation of an initial substituent ? In other words, which substituents can be introduced into an unsubstituted benzene nucleus ?

In answer to this, the following list of substituents will doubtless present itself at once to the reader's mind :

(A)	—Cl,	—Br,	—I,	$\overset{*}{—CH_3}$,	$\overset{*}{—CO}$. CH_3
(B)	$—NO_2$,	$—SO_3H$			
(C)	$—SO_2H$,	—SH			

Very little consideration is needed to show that three types of reaction are involved in the direct introduction of these various

[1] See Holleman, *Die direckte Einführung von Substituenten in den Benzolkern* (1910) ; Obermiller, *Die orientierenden Einflüsse und der Benzolkern* (1909) ; Fry, *The Electronic Conception of Valence and the Constitution of Benzene* (1921).

* These are only two examples selected from the many possible groups which can be introduced by means of the Friedel-Crafts reaction.

substituents. Class (A) contains substituents which are inserted by elimination of a molecule of halogen acid ; Class (B) includes those which can be introduced by the elimination of water ; whilst the members of Class (C) are attached to the benzene ring by an addition-reaction with a rearrangement of the position of the displaced hydrogen atom :

$$\begin{array}{llllll} \text{(A)} & C_6H_6 & + \; Cl\,.\,Cl & = \; H\,.\,Cl & + \; C_6H_5\,.\,Cl \\ \text{(B)} & C_6H_6 & + \; HO\,.\,NO_2 & = \; H_2O & + \; C_6H_5\,.\,NO_2 \\ \text{(C)} & C_6H_6 & + \; SO_2 & = \; C_6H_5\,.\,SO_2\,.\,H & \end{array}$$

Enough has now been said to indicate that even the direct attachment of substituents to the benzene ring presents a series of varied phenomena ; but, curiously enough, these have not yet been subjected to the rigorous investigation which has been devoted to the more complex subject forming the basis of the present chapter. One or two problems immediately suggest themselves for solution. Why, for example, is it necessary to use aluminium chloride as a catalyst for the removal of the very reactive chlorine atom of acetyl chloride during the synthesis of aceto-phenone from benzene and acetyl chloride ? In this case one might expect a ready elimination of hydrogen chloride instead of the sluggish procedure noted in actual practice. Again, how comes it that the benzene hydrogens seem to combine readily with some hydroxyl groups and yet refuse to form water under the action of other hydroxylic derivatives such as the alcohols ? Further, why is the list of substituents formed by addition and rearrangement so short, and what are the factors governing cases of this kind ? We have no satisfactory replies to questions of this type ; for, as will be seen later, the main attention of chemists has been devoted to a more complex side of the substitution problem and the simpler cases seem, in consequence, to have been almost completely ignored.

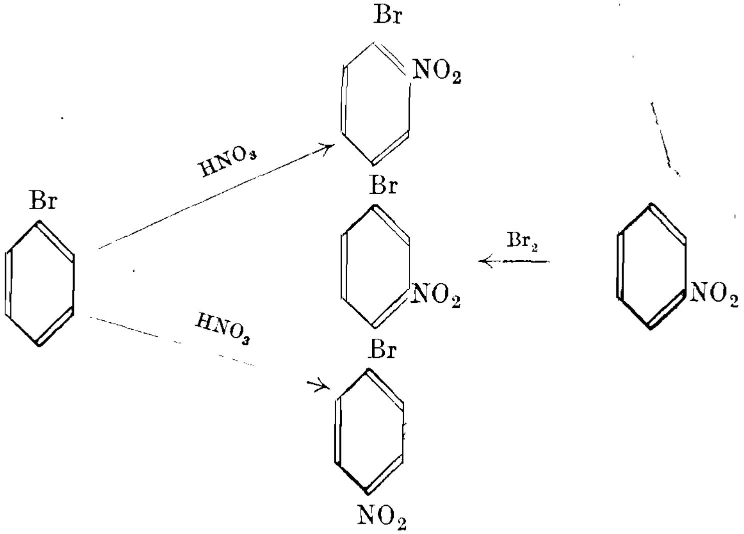
It is now necessary to turn to these more complicated phenomena which have just been mentioned. Instead of taking the case of the benzene ring itself, let it be assumed that a mono-derivative of benzene is under consideration and that a second substituent group is to be inserted into its nucleus. This can be formulated in general terms as follows :

$$C_6H_5\,.\,X \;+\; Y\,.\,Z \;=\; C_6H_4XY \;+\; H\,.\,Z$$

It is evident that there is a choice between three points of attack for the group Y, since it may take up a position with regard to

the initial group X so that an *ortho-*, or *meta-*, or *para*-diderivative is produced. In addition to the benzene ring itself, no less than four factors appear to be involved in the matter: the groups X, Y, and Z, and the displaced hydrogen atom. Each of these might be expected to exercise its influence upon the course of the reaction; and the end-product might naturally enough be supposed to be the resultant of the agencies of all four. In actual practice, the preponderant factor is the nature of the primary substituent X; everything else seems completely subsidiary. Thus it is usual to speak of the *orienting influence* of the initial substituent X, and to regard it as in some way guiding the incoming substituent into a definite position in the ring.

For example, when bromobenzene is nitrated,[1] 35 per cent. of the yield is *o*-nitro-bromobenzene and 65 per cent. is *p*-nitrobromobenzene. Here, obviously, the bromine substituent present has guided the incoming nitro-group mainly into the *para*-position and to a lesser extent into the *ortho*-position; but the *meta*-position has been completely unattacked. On the other hand, when nitrobenzene is brominated, an almost theoretical yield of *meta*-nitro-bromobenzene can be obtained,[2] which shows that the nitro-group guides the incoming substituent exclusively into the meta-position.



[1] Coste and Parry, *Ber.*, 1896, **29**, 788.
[2] Scheufelen, *Annalen*, 1885, **241**, 152.

These examples are sufficient to establish one fact. One type of substituent directs incoming substituents to the meta-position only, but another type of substituent seems to divide its influence between the *ortho-* and *para*-positions. This suggests that in some way the *ortho-* and *para*-positions bear a relationship to each other which is not shared by the *meta*-position.

Having thus brought evidence to show that some substituents act in one way whilst others have a different effect, it is natural to inquire if there is any manner of classifying the possible substituents of benzene into two groups, the one group containing directors towards the *ortho-para*-disubstitution system, the other group comprising those substituents which have a *meta*-directing influence. If this can be done, we shall have an empirical rule to guide us as to where a second substituent will go when it is attached to the ring of a mono-substituted benzene. A further stage would be attained if we could offer some theory which would account for the facts expressed in the empirical rule. For the present, attention will be confined to the empirical side of the problem ; and in a later section an account will be given of the theories which have been put forward to explain the phenomena.

2. *Some Empirical Rules*

The first attempt to generalize on the subject was made by Hübner [1] in rather complicated phraseology which may be translated as follows : " In the replacement of hydrogen atoms during the preparation of polysubstituted benzene derivatives, incoming substituents of a negative (acidic) character go into the *para*-position with respect to the least negative (acidic) substituent already present. They attack the *ortho*-position with almost equal readiness and hence it is usually occupied simultaneously with the *para*-position. From this assumption, it follows that if the benzene ring contains an acidic (negative) substituent, a second acidic substituent will avoid the *ortho-* and *para*-positions and will enter in a position *meta-* to the primary substituent."

Very brief consideration will show that this generalization has

[1] Hübner, *Ber.*, 1875, **8**, 873.

the drawback that it contains two undefined terms: "acidic substituent" and "negative substituent." Obviously if the nitro-group and the bromine atom are to be regarded as belonging to the acidic class, the generalization breaks down at the first test, since a nitro-group orients incoming substituents to the *meta*-position, whereas the bromine atom directs them to the *ortho*- and *para*-positions. Further, as has been mentioned already, the governing factor is the nature of the substituent already present; and the nature of the incoming substituent plays a hardly appreciable part in the problem. Hübner's views, therefore, will not stand examination.

Noelting,[1] a year later, made a much more definite suggestion. According to him, "if the 1-position be occupied by a neutral, basic, or weakly acidic group such as CH_3, Cl, Br, I, NH_2, OH, then the action of Cl, Br, I, HNO_3, and H_2SO_4 will yield as main products the *para*-derivative with an admixture of a lesser quantity of the *ortho*-derivative. On the other hand, if the 1-position be occupied by an acid group such as NO_2, COOH, or SO_3H, then the action of the above-mentioned reagents will lead mainly to *meta*-derivatives with small quantities of the *ortho*- and *para*-derivatives."

Noelting's attempt is obviously better than Hübner's; but it also suffers from that curse of chemical nomenclature—the word "negative" applied to groups. Noelting, for example, classes a halogen atom as "weakly acidic" while placing the nitro-group in the "acidic" series. On such a basis, it would be hard to forecast that benzaldehyde on nitration yields mainly *m*-nitro-benzaldehyde; for the group —CHO does not suggest acidic character at the first glance.

The next effort was made by Armstrong.[2] His view may be expressed thus. Suppose that a mono-derivative has the formula $C_6H_5—X(Y)_n$. If the atoms represented by Y are all monovalent, the incoming substituent will go into the *o*- and *p*-positions; but if any of the Y groups is polyvalent, then *m*-substitution will be the rule. This rule fails, for example, in the case of azobenzene, which nitrates in the *o*- and *p*-positions although both the nitrogen atoms have a higher valency than unity.

We now come to the most interesting of the attempts made

[1] Noelting, *Ber.*, 1876, **9**, 1797.
[2] Armstrong, *J.*, 1887, **51**, 258.

to draw up an empirical rule expressing the rationale of di-substitution. The Crum Brown and Gibson Rule, as it is generally described, will be most easily understood if the words of the authors [1] themselves are quoted.

"We shall best explain our rule by showing how we apply it. We shall write in Column A a number of benzene mono-derivatives, in Column B the radicles replacing one H of C_6H_6, in Column C the hydrogen compounds of these radicles, in Column D the hydroxy-compounds of the same radicles, and in Column E the letters *m* or *o-p* according as the mono-derivatives give *meta-* or a mixture of *ortho-* and *para-*diderivatives.

A.	B.	C.	D.	E.
C_6H_5Cl	—Cl	H.Cl*	HO.Cl	*o–p*
C_6H_5Br	—Br	H.Br*	HO.Br	*o–p*
$C_6H_5CH_3$	$—CH_3$	$H.CH_3$*	$HO.CH_3$	*o–p*
$C_6H_5NH_2$	$—NH_2$	$H.NH_2$*	$HO.NH_2$	*o–p*
C_6H_5OH	—OH	H.OH*	HO.OH	*o–p*
$C_6H_5NO_2$	$—NO_2$	$H.NO_2$	$HO.NO_2$*	*m*
$C_6H_5CCl_3$	$—CCl_3$	$H.CCl_3$*	$HO.CCl_3$	*o–p*
$C_6H_5CO.H$	—CO.H	H.CO.H	HO.CO.H*	*m*
$C_6H_5CO.OH$	—CO.OH	H.CO.OH	HO.CO.OH*	*m*
$C_6H_5SO_2.OH$	$—SO_2.OH$	$H.SO_2.OH$	$HO.SO_2.OH$*	*m*
$C_6H_5CO.CH_3$	$—CO.CH_3$	$H.CO.CH_3$	$HO.CO.CH_3$*	*m*
$C_6H_5CH_2.CO.OH$	$—CH_2.CO.OH$	$H.CH_2.CO.OH$*	$HO.CH_2.CO.OH$	*o–p*

"In Column C we mark with an asterisk those substances which are *not* capable, by direct oxidation, of being converted into the corresponding hydroxy-compounds in the next column, and in Column D we mark with an asterisk those substances which can be formed by direct oxidation from the corresponding hydrogen compounds so that in each horizontal line there is one asterisk and one only, either in Column C or in Column D. By direct oxidation we mean oxidation by one step. Thus, no doubt, $H . CH_3$ can be converted into $HO . CH_3$, but not by one step of oxidation; whereas $H . CO . CH_3$ can by one step of oxidation be converted into $HO . CO . CH_3$. Now it will be seen that wherever the H compound is asterisked, we find *o-p* in Column E, and whenever the HO compound is asterisked, we find *m* in Column E. In other words, when X is naturally to be regarded as a derivative of HX, C_6H_5X gives *ortho-* and *para-*di-derivatives, and when X is naturally to be regarded as a derivative of HOX, C_6H_5X gives *meta-*di-derivatives. Our test by which we determine whether X is to be regarded as derived from HX or HOX is, can HX be directly, by a single oxidizing step, converted into HOX or not? If it cannot, then X is looked on as derived from HX; if it can, then X is to be looked on as derived from HOX."

[1] Crum Brown and Gibson, *J.*, 1892, **61**, 367.

As a concrete example, the chlorination of nitrobenzene may be chosen. Here the substituent is $-NO_2$, and the corresponding hydrogen compound is HNO_2. Since this is directly oxidizable to HNO_3 by one operation, the case will be one of *m*-substitution, and the product of the reaction will be *m*-nitrochlorobenzene. On the other hand, when chlorobenzene is nitrated, the result is different. Here the initial substituent is —Cl and the hydrogen compound is HCl. Now HCl is not convertible into HOCl by a single step in oxidation. The substituent nitro-group will therefore be guided into the *ortho*- and *para*-positions; and a mixture of *o*- and *p*-nitro-chlorobenzene will be formed.

The Crum Brown and Gibson Rule is obviously a great advance upon the ideas of Hübner, Noelting, and Armstrong; but like them, though to a less extent, it has an inherent element of vagueness. Is any limitation to be placed upon the phrase "one step of oxidation"? If this is left unrestricted, then the case of the —OH group will need reconsideration, since at high temperatures the product of the balanced reaction

$$2\,H_2O + O_2 \rightleftharpoons 2\,H_2O_2$$

is found to contain quite measureable quantities of hydrogen peroxide formed by oxidation of water.[1] A similar result is noted when water is subjected to ultraviolet light.[2] On this basis, since water can be converted in one step into hydrogen peroxide, the hydroxyl group should, according to the Crum Brown and Gibson Rule, be a *meta*-orienting radicle, whereas in practice it is an *ortho-para*-directing group. This difficulty might be evaded by extending the phrase in the Rule to "one step of oxidation under ordinary conditions." A further objection to the Rule has been based on the work of Bone and his collaborators[3] who follow Armstrong[4] in believing that the initial stage in the oxidation of methane is the production of methyl alcohol. But as the presence of methyl alcohol during the slow combustion of methane has not yet been established

[1] Nernst, *Z. Elecktrochem.*, 1905, **11**, 710; cf. *Z. anorg. Chem.*, 1905, **45**, 1905. See also F. Fischer and Ringe, *Ber.*, 1908, **41**, 945.

[2] Charitschkoff, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 900; Tian, *Transformations et équilibre chimiques de l'eau et des solutions de peroxyde d'hydrogène à la lumière ultraviolette* (Marseille).

[3] See Bone and Drugman, *J.*, 1906, **89**, 679.

[4] Armstrong, *J.*, 1903, **83**, 1088.

experimentally,* this argument is hardly valid. The behaviour of aniline has also led to objections to the Crum Brown and Gibson Rule in some quarters,[1] but as will be seen later in this chapter, the phenomena in this particular instance are complicated by peculiar factors which demand careful consideration before judgment can be given.

The main objection to the Crum Brown and Gibson Rule lies in its implicit assumption that chemical research cannot discover oxidation methods for converting, say, acetic acid into glycollic acid at a single step. It is, in fact, a pure piece of empiricism based on the facts as known at the time when it was propounded. Quite possibly in most cases it may be correct; but already it seems to have broken down in the case of the hydroxyl group,. and possibly other collapses may follow with an extension of our knowledge. As it stands, however, it forms a very good memory-help; and it undoubtedly suggests that eventually some general principle may be discovered which will cover more cases.

As a final example of these empirical rules, Vorländer's generalization[2] may be mentioned. "In the bromination, sulphonation and nitration of the benzene substitution products $C_6H_5 . E$, the substituents exert effects which are different according as the element of the side-chain is saturated or unsaturated. Chloro- and bromobenzene, phenol, phenetole, toluene, benzyl chloride and phenylacetic acid gave almost exclusively *para-* and *ortho*-substitution products, whereas mainly *meta*-derivatives are obtained from nitrobenzene, benzene sulphonic acid, benzaldehyde, benzonitrile, acetophenone, etc. The radicles which orient an incoming nitro-group into the *meta*-position are unsaturated at the point adjacent to benzene ring:

$$-NO_2, \quad -CN, \quad -CHO, \quad -COOH, \quad -SO_3H;$$

whilst those groups which favour the *para-ortho* type of substitution have a saturated atom next the benzene ring:

$$-Cl, \quad -Br, \quad -OH, \quad -CH_3, \quad -CH_2Cl, \quad -CH_2 . COOH$$

Aniline behaves like phenol."

* Under the experimental conditions, the methyl alcohol, if present at all, would be instantaneously oxidized to formaldehyde. Its detection is therefore hardly to be expected.

[1] See Holleman, *Die Direkte Einführung von Substituenten*, p. 206.

[2] Vorländer, *Annalen*, 1902, **320**, 122.

Here again there is an undefined term in the general statement. What is meant by saying that the element of the side-chain is " saturated " or " unsaturated " ? If the group $—NO_2$ is to be regarded as unsaturated, since it can suffer reduction, what about the $—NH_2$ radicle which can directly attach to itself a molecule of halogen acid ? Again, iodobenzene falls into line with the other halogen derivatives, since in practice it yields both *o*- and *p*-nitro-iodobenzene [1] ; but can it be regarded as having a saturated side-chain in view of the fact that from iodobenzene we can prepare compounds like $C_6H_5 . ICl_2$, $C_6H_5 . IO$ and $C_6H_5 . IO_2$? Obviously Vorländer's use of the word " unsaturated " is likely to produce confusion unless a clear meaning is attached to the expression.

Holleman [2] has collected some test-cases which show the mutually contradictory characters of these various empirical rules and which also permit a comparison between the hypothetical results and the results actually obtained in practice.

In phenylacetic acid, $C_6H_5 . CH_2 . COOH$, the substituent is definitely acidic ; therefore according to Hübner and Noelting, *meta*-substitution should occur. *Meta*-substitution is also predicted on Armstrong's hypothesis, since the atom in the β-position to the benzene ring is a carbon one and hence polyvalent. On the other hand, since acetic acid is not oxidizable directly to glycollic acid, the Crum Brown and Gibson Rule points to *ortho-para*-substitution ; and the same result follows from Vorländer's canon, since the methylene group of $—CH_2 . COOH$ is obviously saturated. In practice, *ortho-para*-substitution is observed.

Turning to the case of phenyl-nitromethane, $C_6H_5 . CH_2 . NO_2$, it is necessary to inquire whether the radicle $—CH_2 . NO_2$ is to be classed as negative or not. Since methyl is reckoned positive and the $—NO_2$ radicle is counted negative, a satisfactory assessment of the character of the group as a whole is obviously not easy. It seems safe, however, to regard it as not belonging to the markedly " acidic " type ; and on this basis according to the Hübner-Noelting hypothesis, *ortho-para*-substitution should be found. On the Armstrong hypothesis, *meta*-substitution is to be expected. Applying the Crum Brown-Gibson Rule, since

[1] Körner, *Jahresbericht*, 1875, 320.
[2] Holleman, *Die direkte Einführung von Substituenten*, p. 207.

nitromethane cannot be directly oxidized to $HO.CH_2.NO_2$, *ortho-para*-substitution is to be anticipated. Finally, Vorländer's canon demands *ortho-para*-substitution also.* Experiment proves that substituents enter in the *meta*-position.

Since the cyanide radicle is only very weakly acidic, the Hübner-Noelting hypothesis suggests that benzonitrile, $C_6H_5.CN$, will yield *ortho-para*-derivatives. On Armstrong's assumptions, *meta*-substitution is to be expected. As HCN is not directly oxidizable to HO . CN (although cyanides can be oxidized to cyanates in one operation) the Crum Brown-Gibson Rule leads to the prediction of *ortho-para*-substitution. Lastly, Vorländer's canon favours *meta*-substitution. In practice, *meta*-substitution is observed.

In the case of acetanilide, all the rules predict *ortho-para*-substitution except Armstrong's, which favours *meta*-substitution. Experiment proves *ortho-para*-substitution.

Finally, take the case of cinnamic acid

$$C_6H_5.CH:CH.COOH$$

Here every one of the rules indicates that *meta*-substitution will occur; yet in practice *ortho-para*-substitution is found.

It is sufficiently clear that none of these empirical rules can stand the test of practice; and the complete breakdown of the whole set in the case of cinnamic acid is striking. Apart from it, the Vorländer canon appears to be fairly successful; and Vorländer's views obviously come near a good attempt to state the facts of the case. But in all these cases the assumption is tacitly made that the entry of a substituent takes place by the mere ejection of a hydrogen atom and the direct entry of the new substituent in the room thus made vacant. As will be seen in the next section, this idea is by no means accurate in every case.

3. *Direct and Indirect Substitution*

In the foregoing examination of empirical rules, it was assumed for the sake of convenience that substitution-reactions are simple exchanges of the incoming substituents for the dis-

* Unless the compound is assumed to react in the *aci*-form $C_6H_5—CH:NO.OH$ in which case Vorländer's canon demands meta-substitution.

placed hydrogen atoms of the benzene nucleus. This process may be termed *direct displacement.* It is doubtful if the mechanism is really so simple as this. A number of cases have been investigated wherein it is clear that more complex processes are involved, although at first sight the results appeared to point to direct substitution. In these cases, the external reagent attacks the benzene derivative at a point different from that at which the new substituent finally attaches itself; and on this account it is usual to describe reactions of this type as cases of *indirect substitution.*

The simplest example of indirect substitution is furnished by the action of hypochlorous acid upon acetanilide, which has been very carefully studied. Witt,[1] by treating acetanilide in acetic acid solution with bleaching-powder, was able to isolate a good yield of *p*-chloracetanilide. At the first glance, this seems to be an obvious case of direct substitution, the chlorine atom simply displacing the hydrogen atom in the *para*-position to the group $CH_3 . CO . NH—$. At a later date, it was found [2] that by using solutions of potassium bicarbonate instead of acetic acid, a crystalline material—acetchloranilide—was produced as the primary stage. In this molecule, the chlorine is attached to nitrogen, $CH_3 . CO . NCl . C_6H_5$, and is easily displaced. For instance, when acetchloranilide is treated with potassium iodide in acid solution, the following reaction occurs :—

$$CH_3.CO.NCl.C_6H_5 + 2HI = CH_3.CO.NH.C_6H_5 + HCl + I_2$$

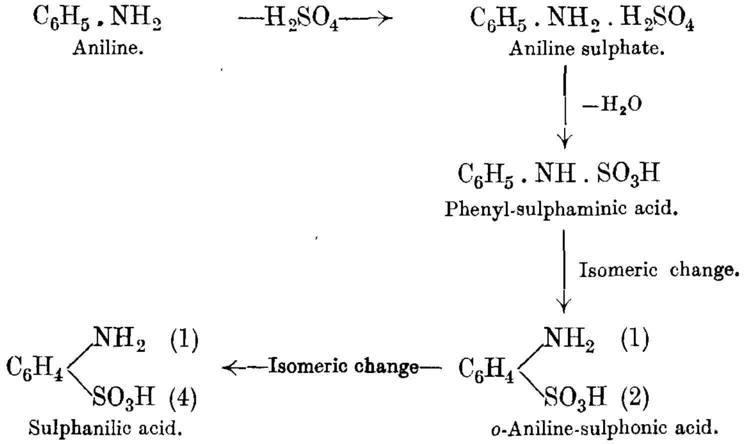
With alcohol, acetchloranilide yields acetanilide, acetaldehyde, and hydrochloric acid.

Now when acetchloranilide is dissolved in acetic acid, it is transformed into *p*-chloracetanilide, the chlorine atom leaving the nitrogen and attaching itself to the benzene ring by the displacement of a hydrogen atom. From this evidence it seems probable that in acetic acid solution, bleaching-powder attacks the molecule at the nitrogen atom and that the acetchloranilide thus produced is then converted immediately by isomeric change into the *p*-chloro-derivative. The application of this reaction to a number of acyl-anilides has been studied by Chattaway and

[1] Witt, *Ber.*, 1874, **7**, 1602; 1875, **8**, 1226.
[2] Bender, *Ber.*, 1886, **19**, 2272; Slossen, *Ber.*, 1895, **28**, 3265.

his collaborators [1]; and it has been shown that the change is a monomolecular reaction.*

Another case in which indirect substitution seems to be beyond doubt is to be found in the sulphonation of aniline.[2] Here a superficial examination might suggest that the process, though indirect, requires only two steps: the formation of aniline sulphate and the rearrangement of this into sulphanilic acid with simultaneous elimination of water. Actually it seems, a much more complicated series of reactions is involved.



The course of the changes appears to rest upon the following basis. In the first place, aniline combines with sulphuric acid to yield aniline sulphate. On heating a mixture of aniline and aniline sulphate, phenyl-sulphaminic acid is formed. In presence of sulphuric acid, this is converted into *o*-aniline-sulphonic acid, which at high temperatures changes into sulphanilic acid.

The case of nitration offers some analogies with that of

[1] Chattaway and others, *J.*, 1896, **69**, 850; 1899, **75**, 1046; 1900, **77**, 800; 1901, **79**, 461; *Ber.*, 1900, **33**, 2398.

* Curiously enough, this labile chlorine atom can be attracted into another molecule. By mixing aniline with acetyl-chloramido-dichlorobenzene, $CH_3 . CO . NCl . C_6H_3Cl_2$, in chloroform solution, the aniline was chlorinated. (Chattaway and Orton, *J.*, 1901, **79**, 461.)

[2] Buckton and Hofmann, *Annalen*, 1857, **100**, 163; Traube, *Ber.*, 1890, **23**, 1654; Bamberger and others, *Ber.*, 1893, **26**, 490; 1894, **27**, 361; 1895, **28**, 401; 1897, **30**, 654, 1261, 2274.

sulphonation, but it appears to be more complex and need not be considered in detail here.[1]

In these examples, it is clear that the initial substituent acts rather like a crane in engineering, since it picks up the incoming substituent group and then, by a second process, transfers the entering substituent to its final position in the ring. As has been mentioned, the intermediate-products have actually been isolated in the cases of the chlorination of acetanilide and the sulphonation of aniline and have been shown to be ordinary molecules of a definite structural formulæ.

In turning to the Friedel-Crafts' reaction, a somewhat different type of intermediate product is encountered: and the case of the synthesis of an aromatic ketone will serve as an example. Perrier[2] showed that when an acyl chloride acts on an aromatic hydrocarbon in presence of aluminium chloride, the action falls into various stages; and his results have been confirmed by Boeseken.[3] In the first stage, two molecules of the acyl chloride unite with one molecule of aluminium chloride. The molecular compound so formed then reacts, in the second stage, with the aromatic hydrocarbon, two chlorine atoms being eliminated in hydrogen chloride. The new molecular compound, built up from the synthetic ketone and aluminium chloride, is then broken up by water and the ketone is thus liberated in the third stage shown below, in which the reaction between toluene and benzoyl chloride has been chosen for the sake of clearness in the formulæ:

$$\text{I. } 2C_6H_5 . CO . Cl + Al_2Cl_6 = (C_6H_5 . CO . Cl)_2,Al_2Cl_6$$

$$\text{II. } (C_6H_5 . CO . Cl)_2,Al_2Cl_6 + 2C_6H_5 . CH_3 = (C_6H_5 . CO . C_6H_4 . CH_3)_2,Al_2Cl_6 + 2HCl$$

$$\text{III. } (C_6H_5 . CO . C_6H_4 . CH_3)_2,Al_2Cl_6 + nH_2O = 2C_6H_5 . CO . C_6H_4 . CH_3 + Al_2Cl_6,nH_2O$$

Analogous phenomena have been detected by Gustavson[4] in the interaction of ethyl chloride, benzene, and aluminium chloride. The reaction is accompanied with marked evolution of

[1] See Bamberger, *Ber.*, 1897, **30**, 1252; Störmer, *Ber.*, 1898, **31**, 2528; Holleman, *Ber.*, 1911, **44**, 704.

[2] Perrier, *Compt. rend.*, 1893, **116**, 1298; *Ber.*, 1900, **33**, 815.

[3] Boeseken, *Rec. trav. chim.*, 1899, **19**, 19; 1901, **20**, 102.

[4] Gustavson, *Compt. rend.*, 1903, **136**, 1065; 1905, **140**, 940; *J. pr. Chem.*, 1903, **68**, 209; 1905, **72**, 57.

heat, and the product has the composition : $C_6H_3(C_2H_5)_3,Al_2Cl_6$. This material has strong catalytic properties. It can attach itself to aromatic hydrocarbons and confer upon them a supernormal reactivity ; for the double compounds formed between it and the hydrocarbons are capable of condensing with alkyl halides by the elimination of hydrogen chloride. No extra aluminium chloride is required for this second stage, and a small quantity of the " catalyst " will serve to activate a relatively large amount of hydrocarbon and alkyl halide. Gustavson's investigations have shown that when mono- and di-alkylated benzenes are required, only the " catalyst " should be present. If an excess of aluminium chloride be added, trialkylation is the result.

Here, obviously, the replacement of the hydrogen atoms in the benzene nucleus is a very complex process ; and in this case the entering substituent is grappled by the aluminium chloride complex compound and not by a substituent group already attached to the benzene ring. The Friedel-Crafts' reaction therefore represents a fresh type of indirect substitution.

There is another factor which enters into questions of indirect substitution and which may even be supposed to influence reactions of direct substitution in some cases. Nitration will furnish an example of the phenomena.

When benzaldehyde is treated with 60 per cent. nitric acid,[1] it yields a colourless unstable oil with a composition corresponding to equimolecular quantities of the two reagents.* Now when this substance is dissolved in acetic anhydride, it yields benzaldehyde diacetyl ester. When dissolved in sulphuric acid, it acts as an auto-nitrating agent, producing *meta*-nitrobenzaldehyde. In a solvent composed of acetic anhydride and sulphuric acid, the auto-nitration again occurs, but this time the product is *para*-nitrobenzaldehyde. Thus the solvent in which the nitration is carried out is by no means a negligible factor in the problem. It is, of course, obvious that if the existence of a directing substituent be assumed, the nature of this orienting group might quite conceivably be modified by

[1] Reddelien, *Ber.*, 1912, **45**, 2904 ; 1915, **48**, 1462 ; *J. pr. Chem.*, 1915, **91**, 213 ; *Z. angew. Chem.*, 1922, **35**, 580.

* This may be a half-ester of the ortho-form of benzaldehyde : C_6H_5—CH(OH)—O . NO_2.

interaction with solvent, as in the case of the sulphonation of aniline; and it is natural to suppose that the case of benzaldehyde nitrate is one in which an influence of this sort actually plays a preponderant part in the course of the reaction.

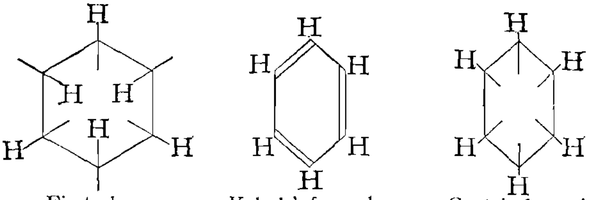
In the following section, some hypotheses will be discussed by means of which an attempt has been made to throw light upon the orientation problem; but the foregoing examples will be sufficient to show that the problem is more complex than it seems at first sight; and this must be borne in mind when any attempt is made to assess the values of the explanations which have been put forward.

4. *Orientation Hypotheses based on Affinity*

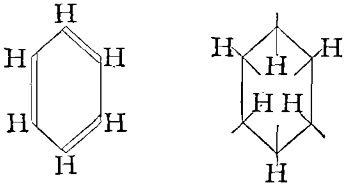
In putting forward their Rule, Crum Brown and Gibson[1] were careful to point out that "it has no visible relation to any mechanism by which the substitution is carried out in one way rather than in another way." In the present section and its successor, a brief survey will be given of some attempts which have been made to suggest a mechanism of substitution. It will be convenient to divide the hypotheses into two groups according to whether chemical affinity is assumed to be a simple attractive force or an electrical traction.

Collie's space formula for benzene[2] is a symmetrical grouping of six carbon atoms each occupying an apex of a regular octahedron and carrying a hydrogen atom. Examination of the model shows that the hydrogen atoms in it are arranged into two sets of three; and Collie assumes a liberation of the carbon atoms such that one triplet of hydrogen atoms is moving towards the centre of the molecule whilst simultaneously the second hydrogen triplet is withdrawing from the centre. The result of the movements of the carbon and hydrogen atoms postulated by Collie is a succession of vibration-phases of the benzene molecule, the plane projections of which can be represented as in the diagram below:

[1] Crum Brown and Gibson, *J.*, 1892, **61**, 367.
[2] Collie, *J.*, 1897, **71**, 1013.

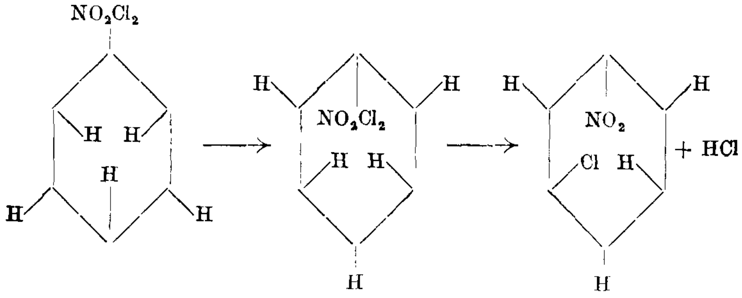


First phase Kekulé's formula Centric formula



Kekulé's formula Last phase

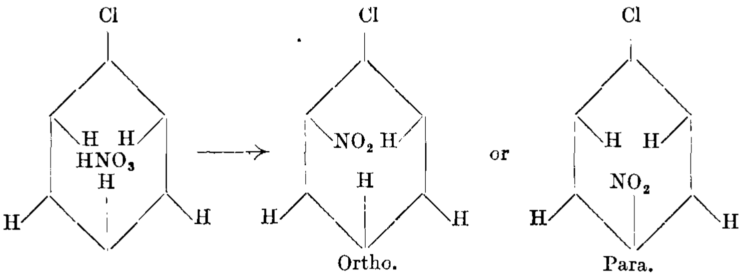
Inspection of these figures will show at once that in the first phase the hydrogen atoms 1, 3, 5 are on the periphery of the structure, whilst in the last phase they have found their way into the central cavity of the molecule. To complete the mechanism of substitution, Collie assumes that certain substituent groups, in virtue of residual affinity, have the power of temporarily holding a molecule of the substituting reagent. By the movement of the carbon atoms, this loose complex is then swept in towards the centre of the molecule and the substituting reagent is thus brought into contiguity with two hydrogen atoms in the *meta*-position. It reacts with these, yielding a *meta*-substitution product. In the case of the chlorination of nitrobenzene, for example, Collie depicts the course of the action as follows:



Here the —NO_2 group has loosely attached to itself the chlorine molecule, as shown in the first figure; then follows

the transport of the complex group into the centre of the benzene system with a consequent close approach of the 3, 5-hydrogen atoms; and finally, one of these atoms is eliminated with a chlorine atom and the remaining chlorine atom enters in position 5 (as shown) or in position 3, so that in either case a *meta*-derivative is produced.

In the case of *ortho-para*-substitution, the mechanism is the same in essentials, though different in detail. Collie assumes that the chlorine atom of chlorobenzene has no attraction for a nitric acid molecule; but that, instead, the nitric acid is attracted by the three hydrogen atoms in positions 2, 4, 6, so that the process follows the course shown in the diagram below:



This gives the main features of the Collie hypothesis. For some further details the original paper must be consulted.

It will be noted that the Collie hypothesis depends upon three main points: (1) the fact that in a perfectly symmetrical space model of the benzene molecule the hydrogen atoms must be arranged in two triplets occupying the 1, 3, 5 and 2, 4, 6 positions respectively; (2) that *meta*-orienting substituents are those capable of forming loose compounds with the incoming reagent molecules; and (3) that in the case of *ortho-para*-substitution the primary substituent has no direct influence while the orienting is actually done by the second triplet of hydrogen atoms.

Now if this conception be applied to the case of cinnamic acid, which has hitherto been a mysterious one so far as we have gone in this chapter, an explanation seems to offer itself. Cinnamic acid undoubtedly contains an unsaturated side-chain to which a molecule of nitric acid could attach itself. Addition of an acid to a double bond usually

takes place so that the non-hydrogen part of the acid molecule enters the α-position, so that the addition-product should be $C_6H_5 . CH(OH) . CH(NO_2) . COOH$. This formulation fits in also with the fact that when nitric acid attaches itself to *αα*-diphenyl-ethylene it yields $(C_6H_5)_2CH(OH).CH_2.NO_2$, wherein the group $—NO_2$ enters in the β-position with regard to the phenyl nuclei. But if this process occurs as a primary stage in the nitration of cinnamic acid, then the actual orienting group will be —CH(OH) . R, since this is directly attached to the benzene ring. The case becomes parallel to that of benzyl alcohol, and this is a compound giving *ortho-para*-substitution, just as cinnamic acid does in practice. It seems, therefore, that the Collie hypothesis is capable of accounting for even this test-case.

In the foregoing discussion of the substitution problem, the benzene system has been regarded implicitly as having a stable arrangement of affinity, but we must now turn to an hypothesis based on redistributions of chemical affinity and see how far that is likely to throw light upon the question.

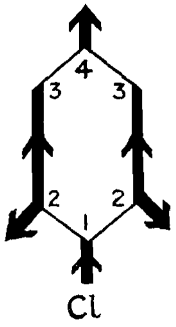
Flürscheim [1] based his hypothesis to some extent upon A. Werner's views [2] with regard to chemical affinity; and his basis may be summarized as follows: (1) There are no such things as directed affinities; chemical affinity is an attractive force acting in all directions from the centre of an atom towards all the points on the atomic surface. (2) The total valency of the atom is a constant for each element; if certain bonds employ large portions of the total affinity-store, there is all the less left over to furnish the remaining bonds by which the atom is attached to others. (3) There is a difference between firm and loose bonds between atoms.

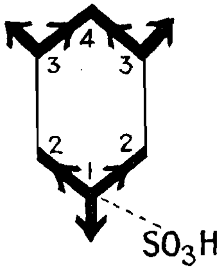
An application of these ideas to a concrete example will make the underlying ideas clearer. Take the case of chlorobenzene. Here the chlorine atom is supposed to cling more tightly to carbon than a hydrogen atom does. Consequently, on the Flürscheim hypothesis, this carbon atom will have less affinity to spare for the rest of its bonds than it had when it bore

[1] Flürscheim, *J. pr. Chem.*, 1902, **66**, 321; 1905, **71**, 497; *Ber.*, 1906, **39**, 2015.

[2] Werner, *Vierteljahresschrift d. naturforsch. Ges. in Zurich*, 1891, **36**, 129; *Neuere Anschauungen auf d. Gebiete d. anorgan. Chemie* (1909 and 1913).

a hydrogen atom. The two *ortho*-carbon atoms, being thus less drawn on for affinity, will each have a larger store of it than they have in unsubstituted benzene. They will therefore have more affinity to spare for the two *meta*-carbon atoms; and these, in turn, will have less than the normal affinity at their disposal for holding the *para*-carbon atom. On the other hand, if the substituent group, say $-SO_3H$, is only weakly held by the carbon atom to which it is attached, then the bonds uniting this atom with its neighbours will be strong ones, the bonds in the 2 : 3 positions will be weak, and those in the 3 : 4 positions will be strong ones. This scheme, according to Flürscheim, makes it possible to work out the relative amounts of affinity left over to attack incoming substituents; and he symbolizes the two systems mentioned above by the following diagrams in which heavy lines represent large drafts of affinity and fine lines indicate slight affinity-demands. The arrow-heads show the direction of the forces which he imagines emanating from the various substituents.





In the case of chlorobenzene, the chlorine atom absorbs a large proportion of the affinity of carbon atom 1, which is thus left with very little affinity for its attachment to the carbon atoms 2 on either side. This is represented by the thin lines. Since very little of the affinity of the carbon atoms 2 is used up in this way, the main portion of it is left over for forming the strong bonds to the atoms 3 and also for a strong attractive force to hold a substituent, as shown by the heavy lines. *Ortho*-substitution would be expected in this case; and if the arrangement be continued round the ring, it will be found that the *para*-atom 4 has also much affinity available to hold a substituent group.

Flürscheim's hypothesis has not stood the test of an examination by Holleman,[1] who has criticized it as follows. In the first place, attraction between atoms must be either akin to gravitational force or else it must resemble electrical attraction. If it is of the gravitational type, then Flürscheim's first assumption of a fixed store of attraction in the atom is impossible since it corresponds to no known phenomenon of gravitation. The earth attracts the moon with a certain force. If a second moon were introduced into the system, it also would be attracted precisely to the same extent as the present one and there would be no reduction of the earth's pull on our existing moon because of the appearance of the new satellite. The electrical type of attraction must now be examined to see if it can be made to fit Flürscheim's postulates. Suppose that A is a positively-charged sphere and that a negatively-charged sphere B is brought near A. The opposite charges will accumulate on the adjacent hemispheres and the averted hemispheres will have very feeble surface charges. So far, the Flürscheim idea seems to fit electrical attraction. If now, however, a third sphere C be brought near B, so that the three spheres are in a line (A—B—C), then if C carries any positive electrical charge, there will be a rearrangement of the electricity on the surface of the sphere B. Thus the distribution of the attractive charges on A and B is not a thing which can be considered in isolation for it may depend markedly upon the character of the charge on C; and if the chain be lengthened, still more interfering factors may be introduced. Thus the "strength" of a given chemical bond is conditioned not merely by the atoms which are united by it but also by the whole of the atoms in the molecule.

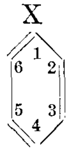
One or two concrete examples will show the errors of the Flürscheim hypothesis. In the first place, take the implicit assumption that some bonds are strong and others weak. Silver nitrate will remove bromine from methyl bromide much more readily than from bromobenzene, which appears to support Flürscheim's ideas, since it suggests that the strength of the bonds joining bromine to carbon is different in the two organic molecules. But in the formation of the Grignard reagent it is found that magnesium acts with equal ease upon methyl bromide and bromobenzene; so that no difference in reactivity is noticeable.

[1] Holleman, *Die direkte Einführung v. Substituenten*, p. 210.

This shows that the nature of the reagent used to remove the bromine is the dominant factor and that the supposed variation of bond-strength need not be postulated at all. Again, the nitro-group is one which seems to be firmly attached to the benzene ring in most cases ; but when other substituents are introduced into the molecule, it becomes easily displaced. Thus tetranitro-resorcinol is hydrolyzed by water with the elimination of nitrous acid and the production of trinitro-phloroglucinol, which shows that the carbon-nitrogen bond is here extremely feeble. Finally, the halogen atom of bromobenzene may be rendered perfectly labile by nitrating the phenyl nucleus. From these examples, it is evident that the strength of a bond depends on the constitution of the molecule as a whole and, further, that in estimating the strengths of bonds the nature of the external reagent employed has a great influence on the results.

Hypotheses resembling that of Flürscheim have been suggested by Tschitschibabin [1] and by Obermiller [2] but it is unnecessary to deal with them here.

Holleman's ideas [3] must now be described. In the Kekulé formula for benzene, a substituent, X, is always attached to a carbon atom joined to its neighbour by a double bond—



Now a substituent in this position is known to manifest low reactivity, as can be seen by comparing the difficulty of removing chlorine from $CH_2{=}CCl{-}CH_3$ and the ease with which the halogen atom is extracted from $CH_2{=}CH{-}CH_2Cl$. Since the double bond has an influence on the halogen atom, Holleman believes the converse to be true, so that the character of the double bond is affected by the nature of the substituent X. The important difference, according to Holleman, is to be found in the effect of the substituent in making addition to the double bond easier or more difficult than in normal cases ; and since

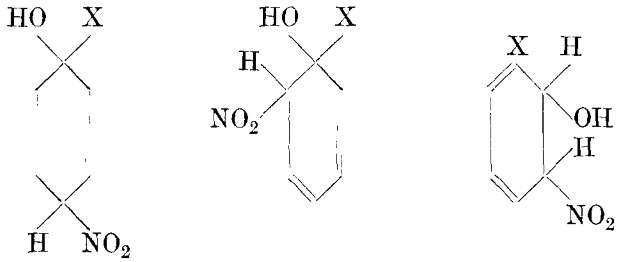
[1] Tschitschibabin, *J. pr. Chem.*, 1912, **86**, 397.

[2] Obermiller, *J. pr. Chem.*, 1907, **75**, 1 ; 1908, **77**, 65 ; *Orientierenden Einflüsse u. d. Benzolkern* (1909).

[3] Holleman, *Die direkte Einführung* etc., p. 476 ff.

the double bond is part of a conjugated system, the influence of the substituent will extend down to the 1, 4-position as well as to the 1, 6-position. The double bond in the 2, 3-position will not be affected by the substituent X, except indirectly.

Holleman assumes that substitution in benzene takes the form of an addition reaction followed by elimination. On this basis, the action of nitric acid on C_6H_5X may have as its first step the formation of any one of the following three structures :—



Para. Ortho. Meta.

The second stage is the elimination of water from the various structures.

Obviously the type of the reaction-product will depend mainly on the relative velocities of formation of the three structures shown above. If X influences its adjacent double bond in such a way as to make it more active than a normal benzene double bond, then the addition will take place as shown in the central formula and probably also as in the left-hand formula. If, on the contrary, X has a depressive effect on the adjacent double bond, then the addition-compound formed will be that shown on the right. Now since the left-hand and central formulæ lead to *ortho-* and *para-*substitution by elimination of water, whilst the right-hand formula results in *meta-*substitution, the bearing of Holleman's ideas becomes evident. The action of the substituent X, according to him, is concerned with the reactivity of the double bond to which it is adjacent. If the double bond is stimulated into extra activity by the presence of X, we get *o-p-*substitution ; but if the reactivity of the double bond is depressed by the substituent X, then we get *m-*substitution.

Holleman's views are of interest ; but it seems difficult to escape circular argument when applying them. " The nitro-

group is a *meta*-orienting radicle because it depresses the activity of the adjacent double bond. But how do we know that it does this ? Because it orients to the *meta*-position."

5. *Polarity Hypotheses*

The intimate connection between electricity and chemical forces was definitely established a century and a quarter ago by the discovery of Nicholson and Carlisle [1] that an electrical current decomposed water into oxygen and hydrogen, and that these gases, on explosion, reproduced water. In 1807, Davy [2] was led to propound an electrical theory of chemical combination ; and in 1812 Berzelius [3] enunciated his Dualistic Theory which for a time exerted great influence on chemical thought. In his view, each atom possessed two poles of opposite sign, but the amount of electricity was not the same on each pole, so that the element derived its electrochemical character from the stronger pole. This served to account for the fact that certain elements showed positive polarity with regard to some atoms, but negative polarity with respect to others. On Berzelius's assumptions, copper atoms possessed a surplus positive charge whilst oxygen atoms carried negative charges. Combination of copper and oxygen to form copper oxide was the result of mutual attraction of opposite charges ; but since copper oxide is basic, Berzelius made the further assumption that the negative charges of the oxygen were insufficient wholly to neutralize the positive charges on the copper, so that copper oxide still had some remaining positive charges which could bind negatively-charged groups such as SO_3 to form salts.

The next development of interest from our present point of view is due to Crum Brown.[4] He assumed that each atom possessed two kinds of attractive force (positive and negative*), which centred on certain poles of the atoms, monovalent atoms having one pole, divalent atoms being bi-polar, and so on.

[1] Nicholson and Carlisle, *Nicholson's Journal*, 1800, 4, 179.

[2] Davy, *Phil. Trans.*, 1807, **97**, 1.

[3] Berzelius, *Schweigger's Journal*, 1812, **6**, 119.

[4] Crum Brown, *On the Theory of Chemical Combination* (1879).

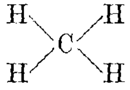
* These terms are used for convenience. Crum Brown did not definitely ascribe electrical character to his hypothetical forces.

Chemical combination is the result of an attraction between opposite poles.

Now when two hydrogen atoms combine with an oxygen atom, the forces of the oxygen atom were assumed to be equally divided between the two hydrogen atoms, since these two atoms are exactly alike. A potassium atom was assumed to have a greater store of positive force than a hydrogen atom possesses. Thus if one of the hydrogen atoms of water be replaced by a potassium atom, the original uniform distribution of forces will cease to hold. More of the oxygen's negative force will accumulate at the pole next the potassium atom, leaving less of it free to act on the hydrogen atom. This hydrogen atom will therefore be less easily replaced by positive atoms than it originally was in the simple water-molecule.

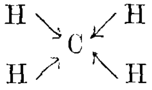
It will be seen that the Crum Brown hypothesis is an attempt to explain how the chemical properties of an atom may be modified by the properties of other atoms which are only indirectly attached to this atom; and following on the lines of Crum Brown we reach a conception of "alternating polarity" which starts from a "key-atom" of known character and progresses along the chain of the molecule, producing at each step an alteration in the distribution of chemical forces.

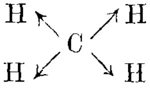
With Sir J. J. Thomson's discovery of electrons, our ideas of the relations between electricity and matter underwent a profound alteration. Thomson himself [1] put forward the view that a chemical bond came into existence by the transfer of an electron from one atom to another, the transferring atom becoming thus positively electrified whilst the accepting atom gained a negative charge. The ordinary valency lines of graphic formulæ would thus be interpreted as tubes of force starting from the positive atom and ending at the electron on the negative atom. There is this difference, however, between the tubes of force and the original chemical bond—the tube of force has an element of direction which is lacking in the usual conception. Thus methane can be written in only one way in graphic formulæ:



[1] Thomson, *Corpuscular Theory of Matter* (1907).

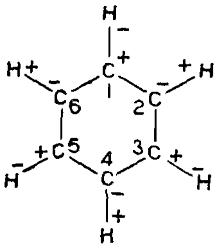
whereas on Thomson's scheme two possible types of methane can be imagined, according as we suppose the electrons to leave the hydrogen atoms and land on the carbon atom, or *vice versâ.*





This hypothesis of Thomson was developed with reference to organic compounds by Falk and Nelson[1]; and has been applied by Fry[2] to the problem of benzene substitution.

According to Fry, an abbreviated electronic formula for benzene can be represented thus :—



It is assumed that if the hydrogen atoms in positions 1, 3, 5 are negative, those in positions 2, 4, and 6 are positive; and *vice versa.* As a corollary to this, Fry puts forward as a substitution rule for benzene the following : " When the substituents are of the same sign or polarity, they will occupy positions which are meta to each other; if two substituents are of opposite sign or polarity, they will occupy positions either ortho or para to each other."

On this basis, Fry has suggested that the Crum Brown and Gibson Rule can be elucidated in electronic terms. It will be remembered that Crum Brown and Gibson laid stress on the question whether a radicle X should be regarded as derived from HX or from HO . X; and it was seen that our ordinary

[1] Nelson and Falk, *School of Mines Quarterly,* 1909, **30**, 179; *J. Amer. Chem. Soc.,* 1915, **37**, 274; Nelson, Beans and Falk, *ibid.,* 1913, **35**, 1810; Falk and Nelson, *ibid.,* 1910, **32**, 1637; 1911, **33**, 1140; Falk, *ibid.,* 1912, **34**, 1041.

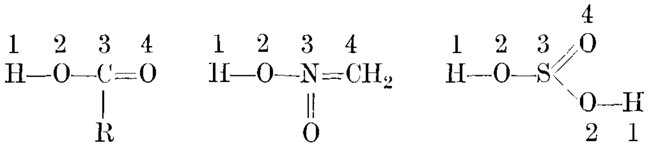
[2] Fry, *J. Amer. Chem. Soc.,* 1912, **34**, 664; 1914, **36**, 248, 262, 1035; 1915, **37**, 885; 1916, **38**, 1323, 1327, 1333; *Z. physikal. Chem.,* 1911, **76**, 385, 398, 591; 1912, **80**, 29; 1913, **82**, 665; 1915, **90**, 458. See Fry, *The Electronic Conception of Valence and the Constitution of Benzene* (1921), for a full account of Fry's views.

formulæ give no help in this matter. According to Fry, from the electronic standpoint, when H is positive and O is negatively divalent, it necessarily follows that X in HX functions negatively, while X in HO . X functions positively.

$$\overset{+}{H}-\!\!-\overset{-}{X} \qquad\qquad \overset{+}{H}-\!\!-\overset{-\,-}{O}-\!\!-\overset{+}{X}$$

Thus a mono-substituted derivative may be either $\overset{+}{C_6H_5}-\overset{-}{X}$, if it is regarded as a derivative of $\overset{+}{H} . \overset{-}{X}$, or $\overset{-}{C_6H_5}-\overset{+}{X}$ if it is looked on as a derivative of $H\overset{-}{O}\text{-}\overset{+}{X}$. Hence when X in C_6H_5 . X is negative and the entering substituent Y is positive, then *ortho-* and *para*-di-derivatives should be formed; whereas when X in C_6H_5 . X is positive and the entering substituent Y is positive, then *meta*-derivatives should be produced.

Some account must now be given of Vorländer's later views.[1] It will be recalled that in formulating the Vorländer Rule * he laid special stress upon the distribution of unsaturated centres in the molecular structure and called attention to the fact that when a double bond lies between the atoms 3 and 4 of a chain, the hydrogen atom in position 1 has acidic properties:



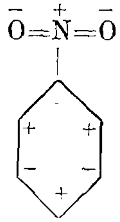
Further consideration led Vorländer to the view that the influence exerted by radicles in a molecule was connected with two factors: the negative and positive nature of the elements of the radicle on one hand, and on the other hand the state of saturation or unsaturation of the radicle.[2]

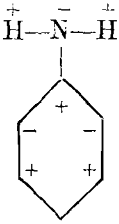
According to Vorländer, the atoms of a radicle may exhibit an alternate polarity which may be symbolized by means of the signs + and — attached to the individual atoms as shown in the formulæ below:

[1] Vorländer, *Ber.*, 1919, **52**, 263.

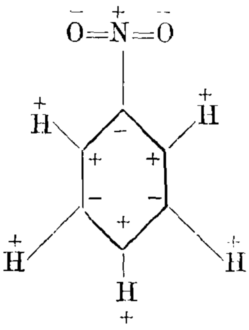
* See Chapter XV.

[2] Vorländer, *J. pr. Chem.*, 1913, **87**, 90; *Ber.*, 1904, **37**, 1646, 1651; 1913, **46**, 3450; *Annalen*, 1905, **341**, 1; 1906, **345**, 155, 251.

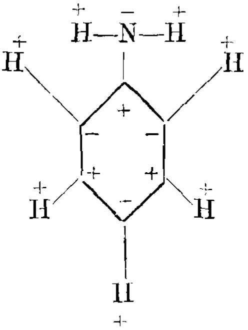




Now Vorländer pointed out that the carbon-nitrogen bonds in these two cases were not of the same type. Since, on his view, hydrogen is a positive atom, the introduction of the nitro-group into the benzene molecule simply means a replacement of one positive atom by a positive complex, since the nitrogen atom of $—NO_2$ is supposed by him to have a positive polarity as shown in the formula above. On the other hand, the nitrogen of $—NH_2$ has a negative polarity induced by the two positive hydrogen atoms which it contains. Hence in the case of nitrobenzene, the general character of the benzene system should be retained, whereas in the case of aniline, the carbon-nitrogen union is different from the carbon-hydrogen union in unsubstituted benzene, and thus a strain is supposed by Vorländer to exist in the aniline molecule. In order to symbolize this, he wrote the nitrobenzene and aniline formulæ with long and short lines to indicate the difference in their natures :



(I.)



(II.)

A glance at these formulæ will show that they indicate a difference between the hydrogen atoms in the *ortho-para* and the *meta*-positions with respect to the substituent. In nitrobenzene, the *meta*-hydrogen atoms are held by negative carbon

atoms, whilst the *ortho-para*-hydrogen atoms are linked to carbon atoms of positive polarity. In aniline, this is reversed. The *ortho-para*-hydrogen atoms are joined to carbon atoms of a polarity opposite to their own, whilst the *meta*-hydrogens are united to positive carbon atoms. Here, then, is a possible mechanism for the explanation of the difference in the substitution-processes in the two compounds.

On the foregoing basis, Vorländer has arranged the commoner radicles into two groups. The members of the first, or "positive group" are those which, like $—NO_2$, can replace a positive hydrogen without change in type. The members of the second class, like $—NH_2$, alter the general character of the benzene nucleus when they enter it as substituents.

Class I. (Positive)

$—SO_3H$, $—NO_2$, —CHO, —CH : NO . OH, —COOH, —COOEt, $—CO . NH_2$, $—CO . CH_3$, —CO . COOH, ≡C . OH,* —C≡N, $—CCl_3$, $—NH_3X$, $—NH_2(CH_3) . X$, $—NH(CH_3)_2 . X$, $—NH_2(CO . CH_3) . X$

Class II. (Negative)

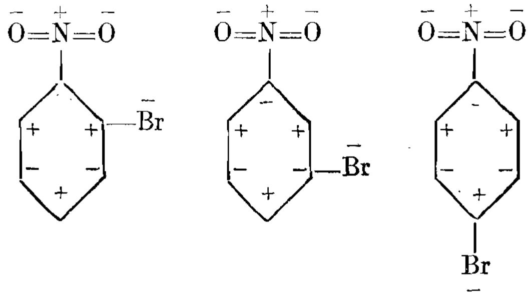
—F, —Cl, —Br, —I, —OH, $—OCH_3$, $—O . CO . CH_3$, $—NH_2$, $—NH . CH_3$, $—NH(CH_3)_2$, $—NH . CO . CH_3$, —N : N—, $—CH_3$, $—CH_2 . CH_3$, $—CH(CH_3)_2$, $—C(CH_3)_3$, $—CH_2Cl$, $—CH_2 . O . NO_2$, $—CH_2 . SO_2H$, $—CH_2 . NH_2$, $—CH_2 . CN$, $—CH_2 . COOH$, $—CH_2 . CH_2 . COOH$, —CH : CH . COOH, $—CH : CH . NO_2$, —C≡C . COOH, $—C_6H_5$

Vorländer has proposed the following explanation of the orientation of incoming substituents, based upon the foregoing conception of alternate polarity. "In the formation of benzene disubstitution products by the halogenation and nitration of benzene monosubstitution-products, the second substituent will be guided by positive elements in the side-chain $C_6H_5—\overset{+}{E}$ mainly into the meta-position and by negative elements in the side-chain $C_6H_5—\overset{-}{E}$ mainly into the ortho-para-position."

A further application of his views has been made by Vorländer to account for differences in reactivity of substituents attached to the benzene ring. According to him, if a negative substituent is attached to a carbon atom of positive polarity, this substituent

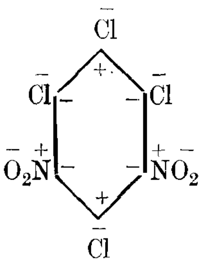
* In the triphenylcarbinol grouping.

will be readily removed and easily replaceable by other negative substituents. For example, the formulæ below show the three nitro-bromobenzenes :



Inspection will show that in the *meta*-compound the negative bromine atom is attached to a negative carbon atom, whereas in the *ortho*- and *para*-derivatives the negative bromine is attached in each case to a carbon atom of positive polarity. On the Vorländer assumption, this would entail a difference in reactivity between the *meta*-bromine and the *ortho-para*-bromines ; and in practice this is found to be correct, since a nitro-group in the *o*- or *p*-position to a bromine atom makes it as labile as the bromine in an aliphatic bromide.

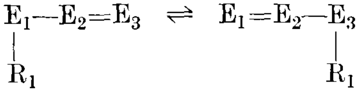
A striking case in confirmation of Vorländer's ideas is to be found in 1, 2, 4, 6-tetrachloro-3, 5-dinitrobenzene :



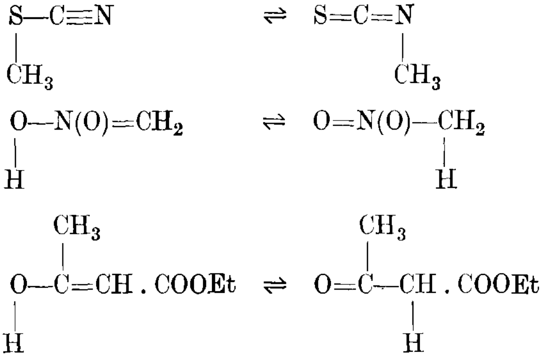
Here it will be noticed that the only chlorine atom united to a carbon atom of opposite polarity is the one in the 1-position. All the remaining three chlorines are united to carbon atoms of negative polarity. Now in practice, the chlorine atoms in the positions 2, 4, 6 can be removed and replaced by groups like $-NH \cdot C_6H_5$ or $-OC_2H_5$, but the chlorine in the 1-position is not thus susceptible.

In 1898, Lapworth [1] put forward a generalization with regard to intramolecular change in organic compounds which is of great interest and which contains a germ subsequently developed by Lapworth into an explanation of orientation processes. He pointed out that intramolecular change is confined to compounds in which certain definite groupings of atoms are present; and it will be convenient to give one or two of these arrangements here.

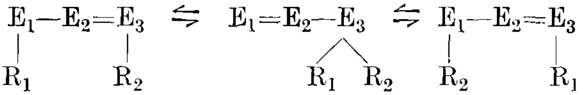
The simplest case can be represented by the general expression:



wherein E_1, E_2, and E_3, represent atoms of elements such as carbon, nitrogen, oxygen, and sulphur, whilst R_1 and R_2 stand for labile substituents attached to these atoms. Concrete examples of such groupings are to be found in thiocyanic and isothiocyanic esters, in the normal and *aci*-forms of nitroparaffins, and in the two possible forms of acetoacetic ester:



A slightly more complex case is that in which each of the terminal atoms of the system $E_1—E_2{=}E_3$ carries a labile substituent. Here the rearrangement is a double one, ending in an exchange of places between the substituents:



[1] Lapworth, *J.*, 1898, **73**, 445.

Lapworth symbolized this in tetrahedral models in the nanner shown in Fig. 1. From our present standpoint, the nain interest lies in the fact that there is an exchange of sub-.tituents between the α- and γ-carbon atoms, which has led o the rearrangement being described as the $\alpha\gamma$-rearrangement.

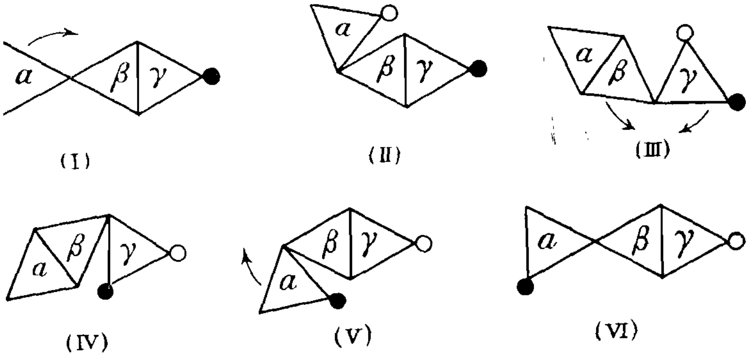


FIG. 1.

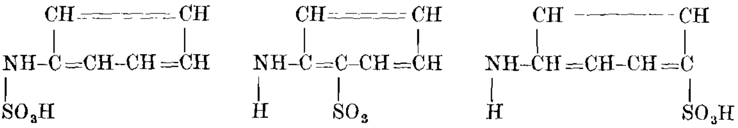
Now suppose that a chain of the type $E_1—E_2=E_3$ is ex-;ended by the attachment of a further group $—E_4=E_5$, by an ınalogous vibration of the carbon atoms all along the chain ;he following changes in the positions of substituents would)e possible :

$$\underset{R}{E_1}—E_2=E_3—E_4=E_5 \rightleftharpoons E_1=E_2—\underset{R}{E_3}—E_4=E_5 \rightleftharpoons E_1=E_2—E_3=E_4—\underset{R}{E_5}$$

\nd in the case where the atoms E_1, E_3 and E_5 all carry hydro-;en atoms or labile substituents, the general expression takes his form :

$$\underset{R_1}{E_1}—E_2=\underset{R_2}{E_3}—E_4=\underset{R_3}{E_5} \rightleftharpoons \underset{R_2}{E_1}—E_2=\underset{R_1}{E_3}—E_4=\underset{R_3}{E_5} \rightleftharpoons \underset{R_2}{E_1}—E_2=\underset{R_3}{E_3}—E_4=\underset{R_1}{E_5}$$

This last form of the general expression is interesting, since t fits very neatly the case of the sulphonation of aniline which vas described earlier in this chapter. For the sake of parallelism, he benzene ring may be distorted as shown below, and the epresentation may be begun after the formation of the phenyl-ulphaminic acid which is known to be the second stage in ulphonating aniline :



Phenyl-sulphaminic acid. *o*-Aniline sulphonic acid. Sulphanilic acid.

From the $\alpha\gamma$-Rule, Lapworth[1] was led on to what he termed the principle of induced alternate polarities in chains of atoms. According to Lapworth's views, "the laws of change in carbon compounds are the (mathematically) necessary results of the operations of the laws of valency applied to the migration of the point or condition of free valency arising from a dissociation akin to ionization." These considerations "indicated that the alternate atoms in such a chain" (of carbon atoms) "might be expected to exhibit similar powers of acting as seats of ionic activity"; or, to use a phraseology now familiar in such connexions, the alternate atoms might be expected to show similar "polarities."

Lapworth assumed that "each atom in its organic chemical combination can be associated with a given (maximal) number of bonds or valency lines; that, whilst any atom may not have more than this maximal number associated with it, it may have less; and, lastly, that the total number of these bonds or valency lines (whole+fractional) in any part of the molecule remains constant unless there is definite reason to postulate that some have passed to or from another part of the molecule or to or from the surroundings."

The postulates of Lapworth "permit of a great variety of modes in which valencies may be adjusted after a disturbance, some of these modes being dependent on the original disturbance and others not. . . . When any disturbance takes place in the number of shared valencies which are associated with an atom in its normal state of combination, then a constraint is usually set up and the atom strives to regain its normal condition. This may lead to a redistribution of valencies elsewhere; but in the consequent changes due to the propagation of the strain along any part of the molecule, the strains at all points in that part taken together cannot exceed the original constraint in

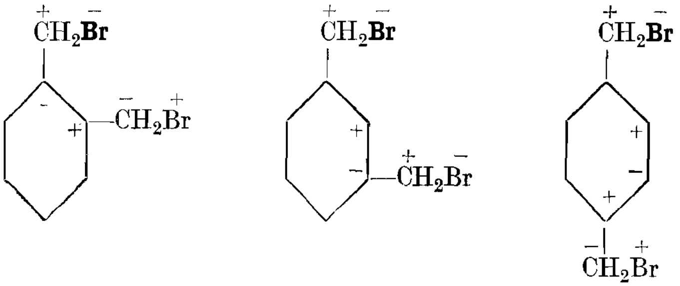
[1] Lapworth, *J.*, 1901, **79**, 1265; *P.*, 1901, **17**, 93; *Mem. Manchester Phil. Soc.*, 1920, **64**, ii, 1; *J.*, 1922, **121**, 416; Burkhardt and Lapworth, *J.*, 1925, **127**, 1742.

that part. (The chances of a second disturbance arising independently at another point in the same molecule are small unless the first is so prolonged as to assume a static character, and . . . the results of a single initial disturbance only are considered.)"

A further extension of these ideas brings us to the conception of "the key-atom." It should be noted that Lapworth lays down the rule that the term "key-atom" should be applied only to the atom which is considered to be responsible for a certain effect and not merely to one which produces the most striking effects or even to one which has an effect on every property. The "key-atom" in fact is not always the same in the same compound, but is any atom to the alternate inductive effect of which certain properties of the molecule are due. Thus in considering the properties of formic acid sometimes oxygen and sometimes hydrogen was considered to be the "key-atom." The effects of two "key-atoms" may be superimposed or may so operate that each in turn may determine the properties in different phases of the same molecule.

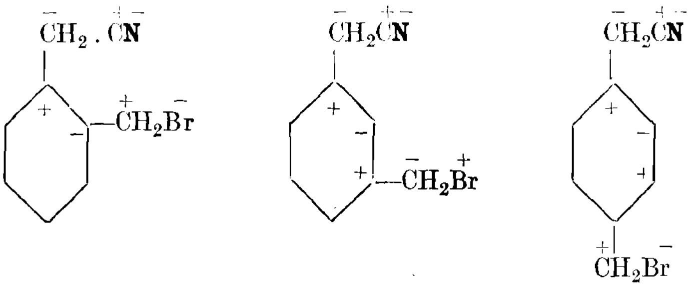
Very little consideration will show that Lapworth's postulates lead to the same results in practice as those of Vorländer, which have already been analyzed; so it is unnecessary to go over this ground again in detail. Instead of that, two fresh cases may be discussed which are of interest.

Gough and Thorpe[1] observed that when *o*- and *p*-xylylene dibromides interact with potassium cyanide in alcoholic solution, the end-products are dicyanides; and no monocyanide was isolated in either case. On the other hand, *m*-xylylene dibromide under the same conditions easily yields a monocyanide. Here the heavy-type bromine atom is taken as the "key-atom" and the alternating polarities in the three dibromides are shown in the formulæ below:

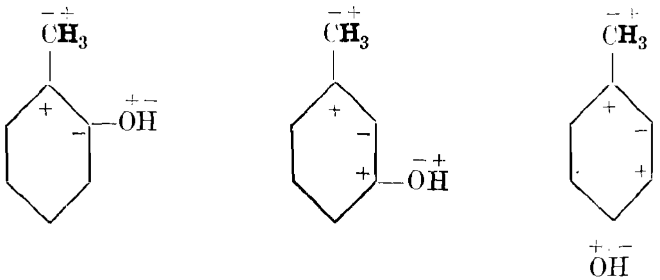


[1] Gough and Thorpe, *J.*, 1919, **115**, 1155.

Now when a cyanide radicle is introduced instead of this bromine atom, the new "key-atom" is the nitrogen atom shown in heavy type; and it will be seen at a glance that this change in the "key-atom" enhances the "negativity" of the bromine atoms in the *ortho-* and *para*-compounds, but tends to neutralize the normal negativity of the bromine in the *meta*-derivative. This is suggested as the reason for the sluggishness in action of the *meta*-compound's remaining bromine atom, as compared with the activities of the bromine atoms in the *ortho-* and *para*-derivatives.



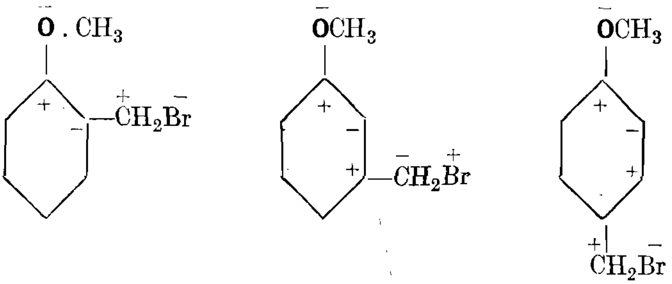
The case of the three cresols is also of interest. Here the assumption is made that the hydrogen atoms of the methyl radicle are "key-atoms"; and on this basis the following schemes of alternating polarities are worked out:



Since hydrogen atoms are assumed to be normally positive, it is obvious that the alternating polarity conception suggests that in *meta*-cresol the hydroxylic hydrogen has its positivity reinforced, whilst in the *ortho-* and *para*-compounds the positivity of the hydroxylic hydrogens is partly neutralized. This agrees

with the fact that *meta*-cresol has a higher ionization constant than either of its isomers.[1]

Again, when the rates of hydrolysis with alkali are studied in the cases of the three isomeric methoxy-benzyl bromides, it is found [2] that the *ortho*- and *para*-compounds are much more readily acted on than is the *meta*-derivative. The " key-atoms " selected in this case are the oxygen atoms ; and the three schemes are shown below.



Since a bromine atom is normally regarded as negative, it will be seen that the alternating polarity hypothesis indicates a partial neutralization in the case of the bromine of the meta-compound and a reinforcement of the negativity in each of the other cases.

It should be noted that these two reactions, taken together, are intended to indicate that the properties of the bromine atom in the last case is influenced by the oxygen of the methoxyl group, whilst in the previous example, the ionization of the hydroxyl group of the cresol was affected by the methyl radicle. The two cases therefore have been put forward by Lapworth as complementary.

It cannot be denied that the alternating polarity hypothesis fits very neatly a large number of cases both in the benzene group and in the aliphatic series. But, on the other hand, it must be admitted that the range of choice which is open in selecting the " key-atom " in certain molecules is an inherent weakness in the application of the idea in practice. In the case of, say, *o*-cyano-benzyl bromide, the two chains of alternating polarities cross if the nitrogen and the chlorine atoms be chosen

[1] Dawson and Mountford, *J.*, 1918, **113**, 937.
[2] Lapworth and Shoesmith, *J.*, 1922, **121**, 1391.

as the respective "key-atoms." Who is to decide which is the correct one? If we let experiment settle the question, then the hypothesis has been of no value in predicting the progress of the substitution reaction employed as a test. It must be borne in mind, as Lapworth himself pointed out, that "polarity theories are acknowledged to be in a state of evolution and at present function properly as aids to interpretation, not as substitutes for intellectual effort."

The problem of alternating polarities has been approached independently by Robinson[1] along a slightly different line. Lapworth developed his ideas on a general basis and thereafter showed how they might be made to agree with electronic views of valency. Robinson's views are based on G. N. Lewis's ideas of atomic structure.*

According to G. N. Lewis's theory, the outer shells of the atoms with which we are here concerned contain respectively the following numbers of electrons: hydrogen=1, carbon=4, and chlorine=7. In chemical combination among the carbon derivatives Lewis assumes that an octet of electrons in the outer sphere of an atom is a stable grouping; and that this total of eight electrons can be obtained by the carbon atom sharing electrons with the other atoms in the compound. On this basis, the ordinary single bond of organic chemistry is represented by a pair of electrons held in common by two atoms; and the ethylenic bond is represented by two such pairs of shared electrons.† Thus the formulæ of methane, ethane, and ethylene are represented as follows:

```
    H             H H              H  H
    ..            .. ..            ..  ..
  H : C : H     H : C : C : H    H : C : : C : H
    ..            .. ..
    H             H H
 Methane.        Ethane.          Ethylene.
```

Now, according to Kermack and Robinson,[2] "if in the

[1] Robinson, *Mem. Manchester Phil. Soc.*, 1920, **64**, iv, 7; 1921, **64**, ii, 17; Kermack and Robinson, *J.*, 1922, **121**, 427.

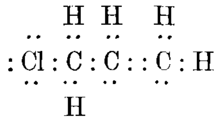
* Kermack and Robinson by some oversight have attributed to Langmuir the ideas initially put forward by G. N. Lewis. A fuller account of Lewis's views will be found in Vol. II.

† This electron-pair is a notable feature in Lewis's theory and differentiates his suggestions completely from those of earlier workers.

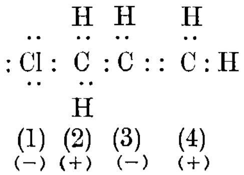
[2] Kermack and Robinson, *J.*, 1922, **121**, 427.

system :A:B:C:D: for some reason internal or external the octet surrounding A becomes stable, this will automatically involve more or less appropriation of the two electrons shared with B, the octet of which is therefore unstable and tends to disintegrate.* If, now, another atom C is attached to B, it will have no difficulty in appropriating two further electrons from B, and in doing so may form a stable octet. This again will preclude a fourth member of the chain D from forming a stable octet. In other words, the atoms A, B, C, and D are respectively, —, +, —, +."

Kermack and Robinson cite the case of allyl chloride as an example, and it may be conveniently presented in a form slightly different from that given by them whereby the change in character of the octets is made clear by a change in the manner of printing the formulæ. In the first place, allyl chloride may be represented as an unstrained grouping of electrons, thus:



Let it now be assumed that the octet around the chlorine atom is stabilized and withdraws two electrons almost completely from the sphere of the adjacent carbon atom. The formula could then be written as below:

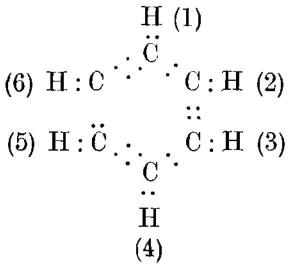


It will be seen that the chlorine atom (1) has now acquired a complete octet of its own by depriving atom (2) of two electrons. The octet of atom (2) having thus become unstable, atom (3) takes the opportunity of attacking it and depriving it of two other electrons to complete its own octet. But with the

* Compare G. N. Lewis, *Valence*, p. 83 (1923).

stabilizing of the octet round (3), the octet of (4) is deprived of two electrons and thus in its turn becomes an unstable group.* Thus along the chain there is an alternation of stable and incomplete octets, by means of which Kermack and Robinson symbolize the alternating polarities of the atoms on their hypothesis.

In the case of benzene, Kermack and Robinson's views lead to the following results. Benzene can be represented on Lewis's formulation thus:



If, now, the hydrogen atom at (1) be replaced by a chlorine atom, a rearrangement of electrons round the ring will take place just as in the case of allyl chloride. As a result, the carbon atoms 1, 3, and 5 will become systems of unstable octets (positive groupings on the Kermack-Robinson view), whilst the carbon atoms 2, 4, and 6 will turn into stable octet systems. Thus the difference in chemical nature between the *ortho-para*-positions on the one hand and the *meta*-positions on the other, is accounted for on these assumptions. In the case of nitrobenzene, on the other hand, if the two oxygen atoms manage to form complete octets, the nitrogen atom becomes an unstable system. Thus the carbon atom (say, 1) to which the nitro-group is attached will be a stable system instead of being unstable as in the case of chlorobenzene. Obviously, in this case, the atomic systems 1, 3, and 5 are stable on this basis, whilst the systems at 2, 4, and 6 are unstable, so that the case is the converse of that of chlorobenzene. On this set of assump-

* Of course things never proceed actually to such an extreme, otherwise the whole molecule would fall apart. The extreme case of a removal of electrons completely from one sphere to another corresponds to ionization; but in the above it is assumed that the process never reaches this ultimate stage and that electron-sharing is still in operation though the "shares" of adjacent atoms are very unequal.

tions an explanation of the different orienting influence of —Cl and —NO_2 could be found.

From this brief summary it will be seen that the views of Lapworth and those of Robinson and Kermack lead to the same conclusions. Kermack and Robinson, however, give a definite conception of the "key-atom" as one which can form a stable octet grouping of electrons at the expense of its neighbours.

6. *Conclusion*

In the foregoing sections, no attempt has been made to include all the speculations which have been put forward from time to time with regard to the problem of benzene substitution. Instead, the aim has been to exhibit some of the very different aspects from which the matter can be regarded and in this way to bring out a number of points which stand in more or less close relationship to the main theme. When a problem is still unsolved, it is often quite as important to know what solutions have failed as it is to learn of those which have been partially successful; for in this way the waste of time involved in useless speculations along hopeless roads is avoided by those who wish to reconsider the problem *de novo* for themselves.

No attempt was made to deal with the orienting influences at work when two or more substituents are present in the benzene ring. This field has been treated by Holleman,[1] who has amassed a great quantity of experimental data on the question. But since the simple case of a single substituent group has not yet been completely cleared up, it seemed unnecessary to discuss the more complex cases here. Enough has been said to indicate some of the numerous points of interest which suggest themselves when the problem is investigated.

[1] Holleman, *Die direkte Einfuhrung von Substituenten.*

CHAPTER XVII

CONCLUSION

IN terminating this volume, it seems of interest to review from a fresh standpoint the various ramifications of organic chemistry which have been described in the foregoing chapters, and to indicate some lines of thought which were less obvious when the subjects were taken up individually and hence were to some extent isolated from each other. A glance at the table of contents will show that the volume has been concerned with five main themes: (1) reagents and their applications; (2) the naturally-occurring substances derived from plants and animals; (3) some new synthetic compounds prepared in the laboratory; (4) certain theories which have been suggested from time to time in order to account for various phenomena; and (5) the historical development of the subject. This grouping of the subjects will enable us to examine each of them in turn and to suggest some ideas which each field in its turn reveals.

In the first place, let us consider the problems suggested by the reagents of organic chemistry. Now at first sight it seems a simple matter to group these into two main classes: general reagents and specific reagents. The general reagents would be those applicable to a wide range of different types of compounds, whilst the specific reagents would include those which have the power of attacking only one particular atomic grouping in order to form a single specific product. On this basis, oxidizing agents such as chromic acid and reducing agents like nascent hydrogen would fall under the head of "general reagents"; whilst semicarbazide with its specialized application to carbonyl groups, would be regarded as a "specific reagent."

Unfortunately for this method of classification, many of the specialized reagents have properties which would bring

them under the general heading. Phenylhydrazine, for example, is generally employed as a reagent for the carbonyl group; but in addition to this, it has wider applications. Its action as an oxidizing agent is seen in its action upon aldoses, when it converts the secondary alcoholic radicle into a carbonyl group as a preliminary to osazone formation. Again, it has powers as a reducing agent, though its applications in this field are less generally known. It reduces methylene blue to the leuco-compound. It converts nitrobenzene into aniline, according to the following equation:—

$$C_6H_5 . NO_2 + 3C_6H_5 . NH . NH_2 = C_6H_5 . NH_2 + 3C_6H_6 + 2H_2O + 3N_2$$

It has also shown itself capable of reducing azo-derivatives to hydrazo-compounds:

$$C_6H_5 . N : N . C_6H_5 + C_6H_5 . NH . NH_2 = C_6H_5 . NH . NH . C_6H_5 + C_6H_6 + N_2$$

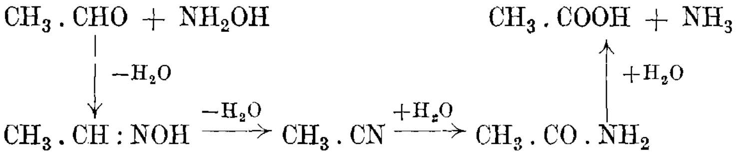
Sometimes the reaction can be carried to the stage at which the azo-compound is split into two amino-derivatives:

$$NH_2 . C_6H_4 . N : N . C_6H_5 + 2C_6H_5 . NH . NH_2 = NH_2 . C_6H_4 . NH_2 + H_2N . C_6H_5 + 2C_6H_6 + 2N_2$$

Another of the specific agents for the carbonyl radicle—hydroxylamine—has an analogous series of properties; and since these are to some extent concealed by our normal methods of regarding each reaction in a series as separate from the rest, it seems of interest here to draw attention to the matter. Although hydroxylamine is generally regarded as a specific agent for the carbonyl group, its action on the carbonyls in the quinones is quite different from normal oximation, if the conditions be properly chosen. An excess of hydroxylamine in alkaline solution acts on quinones as a reducing agent, producing hydroquinones.[1]

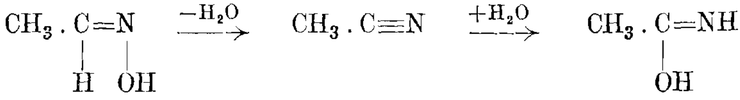
On the other hand, hydroxylamine may be made to play its part in a process of oxidation, as is shown in the scheme below:

[1] Goldschmidt, *Ber.*, 1884, **17**, 213; Valeur, *Ann. Chim. Phys.*, 1900, (vii), **21**, 500.



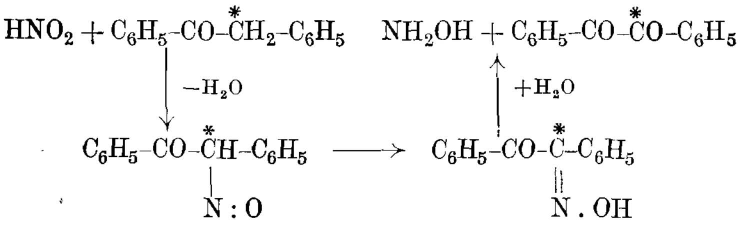
Inspection of this scheme will show that the aldehyde has been oxidized to the carboxylic acid, whilst concurrently the hydroxylamine has been reduced to ammonia ; and it is thus clear that the hydroxylamine has here acted as an oxidizing agent. The immediate recognition of this side of its activity is prevented merely because we are normally accustomed to consider the four reactions above as separate items instead of looking on them as stages in a single process.

This conversion of an aldehyde into an acid by the foregoing method deserves closer consideration. The essential feature of the process is the transfer of the oxygen atom from the hydroxylamine to the aldehyde ; and it is obvious that this has taken place by the subtraction of two molecules of water in the first pair of reactions and the subsequent addition of two water-molecules in the last two stages. Further examination will limit the mechanism still further, for the crucial processes are to be found in the conversion of the oxime into the nitrile and the subsequent addition of water to form the amide. By writing the formula of the amide in the isomeric form $CH_3 . C(OH) : NH$, it is easy to see how the oxidation is carried out, by inspecting the scheme below :



Clearly the water molecule is removed from the oxime by taking hydrogen from the carbon and hydroxyl from the nitrogen ; but when the nitrile takes up a water molecule, the process is reversed and the hydroxyl group now attaches itself to the carbon atom whilst the hydrogen atom links itself with the nitrogen. This is the obvious mechanism of transferring the oxygen from the hydroxylamine to the carbon compound.

Another reaction of the same type may be quoted here : the action of nitrous acid on a methylene-ketone followed by the hydrolysis of the oxime :



In the first stage a hydrogen atom is removed from the carbo atom marked with an asterisk; in the second stage, during th conversion of the nitroso-compound into the oxime, a secon hydrogen atom leaves this carbon atom; and in the final ste these two missing hydrogens are replaced by an oxygen atom The concurrent process is obviously the reduction of the nitrou acid to hydroxylamine.

Returning to the original question, the classification o reagents, since the attempt to group them as "general" an "specific" obviously fails, it might be supposed that a bette system might be found by arranging them under the head "synthetical reagents" and "analytical" reagents. In certai cases, this would serve very well. For instance, the Grignar reagent can be employed only to add extra radicles to existin complexes, and can never be utilized as an agent for breakin up a compound into simpler groupings. On the other hand hydriodic acid is utilized for the removal of certain atoms o groups from an existing molecule and might therefore reason ably be termed an analytic reagent. But here again, close examination proves the faultiness of any such classification Oxidizing agents are mainly analytic in their action; but i the case of ethylenic compounds they may actually serve t introduce hydroxyl groups into the molecule, which would brin them under the head of synthetic reagents. So many othe cases of dual action are known that it is quite impossible t draw any rigid line between synthetic and analytic reagents.

Considerations of this kind may at first sight seem to lea to very little result; but actually they point to something o considerable importance. They suggest, in fact, that ever chemical reaction must be considered from two points of view first, in its relation to the general processes of organic chemistr as a whole; and, second, as an individual case apart from an

preconceived scheme. In the earlier days of organic chemistry the main effort was directed towards bringing order out of what seemed a mere chaos; and naturally the main stress was then laid upon analogies and similarities between the reactions of various compounds. Nowadays, having got the science reduced to a stage of almost perfect arrangement, it seems safe to turn back a little and examine our reactions as individuals rather than as mere members of one or other of the classes.

A parallel from the other side of chemistry will help to make the matter clear. In the last century, the inorganic and physical chemists had got into the habit of regarding chemistry as a field for the application of statistical methods. Quite reasonably—in view of the technique of the time—they concentrated themselves upon the results obtainable from a consideration of huge collections of molecules *en bloc;* and the average properties thus studied were believed to be fair representations of the qualities of each individual molecule in the multitude under examination. We now know, owing to the improved methods introduced in the present century, that this way of approaching the subject cannot give us a picture of what really happens, any more than the death-rate of a town can give us the addresses of those who have died within the year. The "chemical atomic weight" 35·5 corresponds to the actual weight of no single chlorine atom, since these atoms weigh either 35 or 37 units. With the coming of the newer methods, inorganic chemistry has developed into a much more refined study than was possible under the statistical system.

Now something of the same kind seems to be overdue in the organic field. In place of attempting to increase the rigidity of our classification, it seems probable that better results might in future be attained by taking things more individually. Instead of endeavouring to bring all hydrolytic reactions together and regarding them as a class, more knowledge might be gained by trying to find out how they differ from each other in detail while still maintaining their general resemblances.

Let us turn now to some of the problems suggested by the carbon compounds which occur in plants and animals. The first point of interest here is obviously the structure of the compound under consideration; for until that is known, only mere guesses can be made in framing hypotheses as to its

behaviour. Here there are two alternative methods available: the analytic and the synthetic. Obviously, in the case of complex compounds, the analytic method is the most promising for a first attack. Examples of it have been given earlier in this volume in the cases of the terpenes and the alkaloids; and it has been shown how, by taking the structure to pieces and identifying the fragments, it is possible to infer the probable constitution of the original molecule. But although in many cases the analytical method leads to a knowledge of the constitution, nevertheless it leaves open in others a loophole for criticism. It will be remembered that even after an enormous amount of work had been done upon camphor, the formula of that substance was still left in dispute.

At this point the synthetic method comes in. It is possible in many cases to synthesize a compound having the structure suggested by the analytical method; and if this synthetic product proves to be identical with the natural substance, then the constitution is established beyond doubt. The results attained by this method have been illustrated in earlier pages by such examples as Fischer's work in the purine group and Perkin's terpene syntheses, as well as by sundry researches in the alkaloid field.

There is, however, a yet bolder application of the synthetic method which up to the present has been employed with success by Fischer alone. An example of it was given in the chapter on the polypeptides. Here, instead of taking as a goal the synthesis of a single compound, the aim was to advance almost in one leap to the most complex synthetic structures and then, by a comparison between the natural and the synthetic materials, to show the general constitutional type of a whole class of vital products. The success which Fischer achieved by this method among the polypeptides and the depsides is hardly likely to be repeated in modern times. It must be borne in mind that only through a particular form of genius allied to very considerable experimental resources was Fischer able to carry these gigantic investigations to a successful termination; and a fortunate combination of this sort is unlikely to recur at an early date.

The problems suggested by the natural organic products are by no means ended when the structures of the various

substances have been elucidated. At this point, the new subject of biochemistry enters the field and takes up the study of the changes which the materials undergo in the living organism; and we are led on to speculate as to how the vital machinery has operated in producing these substances, some of which are so simple whilst others are complex in the extreme. This part of chemistry is as yet only in its infancy, despite the enormous amount of investigation which is being carried out at the present time; but already it has become clear that some of the most interesting parts of organic chemistry will be developed in future largely on the biochemical side. Already it is possible to foresee that a better knowledge of enzyme action may easily work a complete revolution in some parts of our laboratory technique; and the study of the reactions which proceed at ordinary temperatures in the vital organism may throw a flood of light upon our views of syntheses and decompositions.

We may now pass to questions suggested by the purely synthetic side of organic chemistry. The subject has long passed the stage when any human mind could be expected to retain the details of even a single specific property—such as the melting-point or the boiling-point—of each of the enormous number of carbon compounds which have been carefully recorded in our literature. It is self-evident that the vast majority of the known synthetic substances have already served the only purpose of their existence—the publication of a paper—and that henceforth they will be allowed to rest undisturbed, since no one will have the slightest reason for investigating them. This may seem to discourage the synthetic side of the subject; but in order to hold the balance evenly it must be borne in mind that we owe to the synthetic method a number of compounds which have a real interest and which we could ill spare. Even the most obvious synthetic reactions may lead to wholly unexpected results, as in the case of the first synthesis of a triphenylmethyl derivative; but it must be admitted that the proportion of interesting substances to mere "gap-filling" compounds is very small indeed.

As examples of compounds which have an interest apart from their melting-points, we may mention here the ketens, the aliphatic diazene derivatives, the polypeptides, the polyketides, and the triphenylmethyl series, all of which have

been described in earlier chapters of this volume; and to them may be added the depsides, the alkali-aryls, the metal-ketyls, the spirane group and other compounds which have thrown light on stereochemical theory. The discovery of each of these classes has had its reaction upon our general views in one branch or other of organic chemistry; and if all reference to them were deleted from the literature, the face of the subject would be considerably modified. On the other hand, if penta-triacontane, $C_{35}H_{72}$, were to disappear from print to-morrow it is safe to say that few would miss it and no sensible chemist would suffer much grief over its loss.

Before closing this survey, something must be said with regard to a side of the subject which is at present more neglected than it should be: the historical branch of organic chemistry. Owing to the manner in which the modern development of organic chemistry is condensed in most text-books on the history of chemistry, it is difficult for the student to obtain a good conspectus of the progress of the science in the last generation. This is most unfortunate, for the advances made since 1880 or thereabouts actually furnish a very complete education in the methods by whch the subject has been clarified and amplified.

In studying the history of organic chemistry, two courses can be adopted. In the first, a single subject may be selected and its gradual development may be traced out as investigator after investigator contributed his share to the advancement of our knowledge. This is one of the most fascinating ways in which a sound acquaintance with organic chemistry can be gained; and if it be pursued with intelligence, it lends to the subject a perspective which can never be derived from the mere study of text-books. As a guide in this branch, the only book is Lachman's *Spirit of Organic Chemistry*, which sketches the history of the main themes which were under investigation between 1880 and the opening of the present century. Any reader who is really interested in the subject will find Lachman's book quite as enthralling as the average detective story; and it seems a great pity that it has not been supplemented by a second volume dealing with more recent developments.

There is a second method of reading this history of organic chemistry; for we may take the career of a single investigator and endeavour to trace out how he passed from one line of

research to another, and in this way try to put ourselves in his place and see how he was led on logically from problem to problem.

As an illustration of this, the career of van't Hoff may be sketched in its bare outlines. In his student days, he evolved the idea of stereochemistry and extended the then existing structural chemistry into three dimensions. His next step is seen in his *Ansichten über die organische Chemie* where, amid the discussion of chemical structures, the idea of reaction-velocities made its appearance. Three years later, this found a fuller expression in his *Etudes de dynamique chimique;* and the experimental work which was carried out by him in this field brought him face to face with the problem of chemical affinity. Here the affinity which unites the components of double salts attracted his attention and led to his discovery of transition temperatures. A second line of thought from the same starting-point brought him to consider the wider problem of solution and led to his enunciation of the osmotic pressure theory. And in his final completed research he again set out from this same jumping-off ground in order to elucidate the intricate problem of the oceanic salt deposits. From this it is easy to see that van't Hoff proceeded logically from one line of research to its successor; and that his ideas were all of that big and simple type which bear the mark of genius at work.

Another example of the same kind may be drawn from part of Fischer's career. In an earlier chapter it has been shown how he developed the methods of synthesis in the field of the polypeptides, using the amino-group of one amino-acid to form an amide with the carboxyl group of another amino-acid molecule. At the conclusion of his investigation of the polypeptides he was led to examine a parallel series of reactions: the esterification of a hydroxy-acid with the hydroxyl group of a second hydroxy-acid. In this way he came into the field of the depsides; and so he was led to approach the moss acids and tannin from the synthetic side. Thus the examination of one series of reactions drew him forward into a fresh field, and this, in its turn, opened out into a completely new region of the subject.

It will be seen from the foregoing that historical chemistry has a double interest. On the one side, it furnishes us with an

account of the development of a single theme in the hands of one investigator after another, whilst on the other side it gives us glimpses of the mental transitions whereby a single great researcher passes from field to field during the course of his career. In this last connection, the Memorial Lectures delivered before the Chemical Society and the obituary notices published by the Deutsche Chemische Gesellschaft provide materials which are well worth studying. The mere reading of text-books is apt to convey the impression that chemistry is made in some peculiar way apart altogether from humanity; and this is hardly a desirable outlook for anyone to choose. As a corrective to it nothing better can be recommended than E. Cohen's *Van't Hoff* or Hoesch's *Emil Fischer;* for in both these books the interplay of chemical research and ordinary humanity is well brought out. Science, in its essentials, is an adventure in search of knowledge; and an adventure conducted by lay figures in a toy theatre makes much less interesting reading than one in which the hero is a human being like ourselves.

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